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THE MANAGEMENT OF THE PATIENT WITH *Severe Bronchial Asthma*

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INTRODUCTION

THE patient with severe bronchial asthma may be regarded as a psychobiological problem The complicated pathophysiology and disturbed emotional make up require a careful integration of the multiple components which constitute the individual as a whole Proper physiologic management is based upon an understanding of all the *participating forces and their relative values* This calls for specific therapy formulated to minimize or improve disturbed functions and to prevent the irreversible sequelae of the asthmatic state To achieve lasting results considerable rapport in the psychological sense must be developed and the patient must have reassurance without sacrifice of *a determined positive approach on the part of his physician* This requires the continuous education of the patient and his family I know of no other disease which can tax the character and therapeutic ingenuity of the internist as much as the proper management of the very sick asthmatic patient

Whatever the fundamental cause of the asthmatic crisis (liberation of H histamine like substance C acetylcholine like substance or other chemical mediators during the antigen antibody contact) inhibition or neutralization of this substance elimination of mucus which is the product of its action relief of the bronchospasm and finally resolution of the emotional factors which may *precipitate or* modify the attack should be the aim of all therapy The acutely ill patient presents a far more complex problem than that of his specific allergic response Allergically directed therapy should not be regarded as the specific therapy for the management of bronchial asthma *It is* specific only for the management of the underlying allergy when determinable

Contrary to the pessimistic view frequently expressed by the patient and his friends, considerable benefit can be given to the very sick patient with asthma by the application of procedures to be discussed The therapeutic measures suggested are based largely on personal observations in the management of 513 patients and have been correlated

THE PHYSIOLOGIC MANAGEMENT OF THE SERIOUSLY ILL ASTHMATIC

FIGURE 1

with extensive laboratory studies with a large variety of protecting drugs Human assay (protection studies) also have been employed With this new technique, an evaluation of the relative value of new and accepted therapeutic agents for the relief of bronchospasm was possible Furthermore these studies were performed under controlled conditions which are usually not present in the sick patient

In order to restore physiologic balance in the severe asthmatic patient, it is necessary to employ a wide range of properly balanced therapeutic measures I have attempted

to illustrate the various measures which are necessary to balance this therapeutic seesaw (Fig 1) and will discuss the more important ones namely protecting drugs sedation supportive therapy bronchiolar relaxation therapeutic use of gases bronchiolar evacuation or catharsis and the management of infection in the Chapters that follow The relationship of emotional disturbances to the asthmatic paroxysm the value of therapeutic hyperpyrexia and breathing exercises the controversial aspects of climato therapy and finally a variety of miscellaneous procedures not generally recommended will be discussed in somewhat less detail

The manuscript for this book had gone to press when we began our studies with the spectacular pituitary adreno-corticotropic hormone (ACTH) in bronchial asthma The remarkable properties of ACTH and Cortisone and their effects on the antigen antibody mechanism is the subject of considerable study To date we have completed eight acute protection studies with ACTH against the effects of hista mine and acetylcholine in the laboratory and have treated three patients in status asthmaticus with ACTH therapy When successfully employed striking subjective and objec tive improvement appears within one to seven days Treat ment probably may be stopped after the fourth or fifth day in most cases We generally employed 20 mg (Armour units) I M every six hours for the first two days and there after 10 mg every six hours through the seventh day It appears likely that the hormone may be employed in re sponsive patients for maintenance therapy One or two day courses may be necessary at three or four week intervals

In the wake of improvement there may be observed side effects (largely transient) such as mooning of the facies salt and water retention rise in blood pressure hirsutes sense

of well being changes in the psyche and even mild bronchospasm following each injection (due to protein) The modus operandi of ACTH in bronchial asthma is not definitely known The exact changes in histamine metabolism and in the immune mechanism remain to be answered

CONTENTS

LIST OF ILLUSTRATIONS

LIST OF TABLES

THE MANAGEMENT OF THE PATIENT WITH *Severe Bronchial Asthma*

CHAPTER I

THE CLINICAL CONCEPT OF BRONCHIAL ASTHMA

BRONCHIAL asthma is a distressing and common form of acute recurrent or chronic bronchial inflammation and obstructive emphysema usually of allergic origin It is characterized by recurrent cough and a wheezing type of dyspnea in which the patient s main difficulty occurs particularly on expiration The over excitable bronchial mucosa and musculature of asthmatic patients react to factors which generally have no effect on normal subjects Such factors include allergens infection and reflex physical and psychic stimuli It has been estimated that 3 5 per cent of the population are affected with this discouraging and disheartening affliction at some time during life and that 0 2 percent of all deaths in the United States in 1940 were due primarily to bronchial asthma [9] With these figures confronting us it is heartening to note that significant progress has been made in alleviating this condition Analysis of the author s series of cases revealed that approximately 15 per cent were completely relieved 80 per cent were more or less improved and only 5 per cent were resistant to all treatment

1 Pathophysiology

A proper understanding of the physiological mechanisms involved in asthmatic patients during paroxysms and during the asthma free period sheds considerable light on the difficulties attendant upon proper therapy Numerous investigators notably Cournand[57] and Baldwin [8] have dem

CHAPTER I

THE CLINICAL CONCEPT OF BRONCHIAL ASTHMA

Bronchial asthma is a distressing and common form of acute recurrent or chronic bronchial inflammation and obstructive emphysema, usually of allergic origin. It is characterized by recurrent cough and a wheezing type of dyspnea in which the patient's main difficulty occurs particularly on expiration. The over-excitable bronchial mucosa and musculature of asthmatic patients react to factors which generally have no effect on normal subjects. Such factors include allergens, infection, and reflex, physical and psychic stimuli. It has been estimated that 3.5 per cent of the population are affected with this discouraging and disheartening affliction at some time during life, and that 0.2 percent of all deaths in the United States in 1910 were due primarily to bronchial asthma.* With these figures confronting us, it is heartening to note that significant progress has been made in alleviating this condition. Analysis of the author's series of cases revealed that approximately 15 per cent were completely relieved, 80 per cent were more or less improved and only 5 per cent were resistant to all treatment.

1. Pathophysiology

A proper understanding of the physiological mechanisms involved in asthmatic patients during paroxysms and during the asthma-free period sheds considerable light on the difficulties attendant upon proper therapy. Numerous investigators, notably Cournand[illegible] and Baldwin,[illegible] have dem

onstrated significant findings in their subjects During the asthma free period the patient experiences a feeling of general well being and usually evidences no pulmonary distention (increased ratio of residual air to total capacity) Nevertheless the maximum breathing capacity during these remissions is generally 58 per cent of the predicted value[8] and there is evidence of poor intra alveolar ventilation This degree of ventilatory dysfunction is not sufficient to produce signs or symptoms either at rest or upon ordinary exertion

During a paroxysm of asthma however a state of acute ventilatory insufficiency rapidly develops due mainly to inadequate expiration The normally active inspiration becomes more forceful to overcome the diffuse bronchiolar obstruction This results in a greater intrathoracic negative pressure than normal and air passes through the constricted bronchioles into the alveoli The difficult egress of air through the bronchioles during expiration is not as efficiently compensated for Normal expiration is largely a passive process due to the elastic recoil of the lungs and the diminution in chest volume which follows relaxation of the diaphragm and inspiratory muscles During normal expiration the bronchioles shorten and constrict but this degree of constriction is exaggerated in patients with bronchial asthma Expiration being less powerful than inspiration cannot overcome this increased obstruction and so becomes greatly prolonged With fatigue of the accessory muscles of expiration intense bronchoconstriction loss of lung recoil and the poorly functioning diaphragm the lungs become progressively over distended and the chest is held in the position of maximum inspiration

The following changes in ventilatory dynamics and diffusion of gases have been observed in the laboratory the vital capacity as well as the inspiratory and expiratory

velocity rate is decreased the residual air is increased intrapulmonary mixing is reduced and the alveolar oxygen tension and blood oxygen saturation tend to fall while the alveolar and blood carbon dioxide tensions tend to fall[20] in mild or moderately severe bronchial asthma but subsequently rise in more severe and protracted bronchial spasm The lowered vital capacity and slowed inspiratory

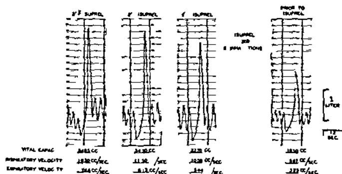


FIGURE 2

and expiratory velocity rates with the striking improvement which follows relief from the underlying bronchospasm may be observed in Figure 2 Finally because of diminished ability for the oxygenation of hemoglobin the amount of reduced hemoglobin in the capillaries rapidly increases and when this reaches a level of 5 gm per cent cyanosis may be observed

Based largely on clinical observations in asthmatic patients and studies with experimental obstructive dyspnea in dogs Barach [20] has contributed greatly to our knowledge of the mechanics of respiration in patients with

bronchial asthma He attributes the initial increase in the asthmatic subjects pulmonary ventilation to reflex stimulation of proprioceptive reflexes in the lungs and chest wall resulting from the physical effort necessary to draw air into the lung Later the consequences of obstructive dyspnea lead to changes in the lung which are responsible for hypoxia which then becomes a contributory cause of dyspnea and in addition exercises a harmful influence When the larynx of a dog was constricted Barach observed an immediate increase in the intrapleural negative pressure during the inspiratory cycle This was obviously necessary for the inward movement of air past the point of obstruction As this pathologically elevated intrapulmonary pressure persists over a long period of time it exercises a cupping action on the pulmonary capillaries and on the intrathoracic bronchi which causes an exudation of serum into the alveoli and an outpouring of mucus from the bronchial mucous membrane Both of these factors interfere with absorption of oxygen With the progressive congestion and edema that followed in the dogs lung Barach observed a marked increase in the physical effort to breathe due both to the original obstruction in the larynx and to an increasingly engorged lung Areas of emphysema appeared in the periphery of the lung and basilar pulmonary edema was finally observed He further demonstrated that when helium oxygen mixtures were breathed under positive pressure of 5 cm of water the pathologically elevated negative intrapleural pressure observed during the inspiratory cycle was markedly decreased and the physical effort of inspiration conspicuously diminished

2 The Acute Paroxysm

The acute paroxysm actually consists of edema of the mucosa and submucosa which may be thrown into folds

accumulation of thick tenacious and copious mucus and spasm of the smooth muscle of the bronchi and bronchioles The attack may vary in intensity from simple tightness or heaviness of the chest to marked dyspnea with characteristically noisy (wheezing) respirations Attacks are more frequent at night At the height of the seizure the patient presents a pitiful sight He sits or stands in a flexed position with his back rounded and his chest shoulders and head fixed This posture tends to increase the effectiveness of his expiratory efforts although it probably reacts to his disadvantage by reducing the lung volume and vital capacity He is drenched with cold sweat and is tense anxious and apprehensive During inspiration the accessory muscles of respiration (sternocleidomastoids trapezii and scaleni) stand out in desperate contraction there is marked retraction in the supraclavicular and intercostal spaces as well as in the epigastrium Expiration is prolonged and labored and requires considerable effort because of increased bronchoconstriction (during this phase of respiration) The diaphragm is usually low and motionless and the chest is seemingly fixed in its over distended position Respirations are ordinarily slow and labored but with infection or in status asthmaticus the rate may increase The asthmatic episode in children especially those under two years of age differs from adults in that the dyspnea is not necessarily expiratory and orthopnea may not be present The acute paroxysm may last for hours or recur in varying degrees of severity for days Finally a state of intractable asthma during which the episode is continuous and refractory to treatment may result

In the initial stage an utterly useless cough may be present (tussic insufficiency) Later however sputum which is thick and tenacious or mucoid and frothy is expectorated This material is generally whitish but may become grayish or yellow As the episode progresses the

sputum generally becomes thinner and with improve ment it is more easily expectorated An effective cough ing paroxysm may liberate a large plug of mucoid sputum which may herald relief *Hemoptysis in the* absence of other pulmonary disease is very rare Anorexia and vomiting may occur Although the temperature is usually normal or often subnormal fever may be present *especially in children and in adults with associated infec* tion There may also be an increase in the white blood count as well as in the number of eosinophils in both the blood and the sputum

Examination reveals distant breath sounds prolonged expiration and the typical music box revue (sonorous and sibilant dry rales and rhonchi of varying grades of intensity) Moist rales are rare unless associated with pneumonitis atelectasis or bronchiectasis The percussion note is usually *hyper* resonant and *the heart sounds* are distant due to varying degrees of emphysema

3 Complications

In the severe persistent acute episode or in the continu ous paroxysms of status asthmaticus the patient presents a picture of marked physiological imbalance Evidence of severe hypoxia cyanosis dehydration peripheral vascular collapse and drug intoxication from previous intensive therapy may *be present Death may come suddenly from* any of the latter factors but more commonly in status *asthmaticus it is due to* asphyxia resulting from plugged and obliterated bronchi and bronchioles Death may also be brought on more quickly by the injudicious use of mor phine and other drugs

Complications in the course of the acute attack are few *Pleurisy subcutaneous emphysema mediastinal emphy* sema spontaneous pneumothorax segmental atelectasis

and heart failure (both right sided and total) may be observed Gradually with repeated and prolonged attacks pathological changes typical of emphysema appear in the structure of the lungs and thorax The smaller bronchi and the alveoli may be more or less enlarged depending upon the degree of emphysema McMichael[118] considers emphysema as the commonest cause of pure right heart failure (pulmonary heart failure) He believes that poor ventilation of the lungs due to hypoxia induces vaso constriction of the pulmonary arteries and pre-capillaries Right sided heart strain is largely the result of this pulmo nary hypertension In the chronic state other changes in the lungs may be observed namely bronchostenosis bronchiectasis atelectasis and non specific pulmonary in filtrations and bronchopneumonia

Progressive obliterative endarteritis of adjacent pulmonary blood vessels may occur in a number of primary diseases of the lung Barden and Cooper[30] have described the roentgenologic manifestations of a great variety of diseases which affect the peripheral blood vessels of the lung Rich and his associates[93, 146, 147] have experimentally reproduced the characteristic response of the peripheral pulmonary vessels to a hypersensitivity state and have called our attention to the wide variety of diseases in which this non specific reaction may occur Harkavy[88, 89] de scribed reversible changes in some forms of bronchial asthma in which the pulmonary vessels act as shock organs With increased sensitization a progressive necrotizing obliterative endarteritis of the smaller pulmonary vessels appears The pathological lesions found in patients with histories of acute onset of bronchial asthma without de monstrable cause and with essentially negative skin tests and clinical courses characterized by fulminating broncho-spastic crises are frequently indistinguishable from the

lesions found in a great variety of clinically and etiologically different conditions (sulfonamide sensitization fatalities serum sickness lupus erythematosis acute rheumatic fever periarteritis nodosa and others) The response *which is the same in all of these varied* ailments namely an increased pulmonary capillary permeability (of the pulmonary vessel wall to serum and protein) *resulting in* patchy or massive edema of the lungs certainly suggests a common denominator The restricted ventilatory capacity due to bronchospasm emphysema and these peripheral vascular changes in the lung produces pronounced symptoms of respiratory insufficiency which may lead to death in the asthmatic subject

4 Fatalities

The first major study of the pathology of this disease by Huber and Koessler in 1922 was followed by many individual case reports Significant recent reviews have been made by Rackemann[139] Unger[10] and Gay[85] A possible relationship between bronchial asthma and the general *adaptation syndrome (Selye) has been suggested* by many observers According to the thesis of the general adaptation syndrome the so called diseases of adaptation follow the continued stimuli of a series of alarm reactions over an extended period of time[115 176] Among these diseases of adaptation Selye includes hypertension periarteritis nodosa rheumatic fever and glomerulonephritis Selye[176] has *reported the results of* various workers who have been able to produce the alarm reaction in animals by different stimuli employing such agents as epinephrine histamine decreased oxygen tension and emotional stress The morphologic changes observed in animals during the alarm reaction are best noted in *the lymphoid tissue and the* adrenal glands Bronchial asthma appears to be a disease

in which a number of alarming stimuli occur during an attack From the nature of the disease many attacks occur over a long period of time If the theory of the diseases of adaptation can be applied to man one might well expect to find in bronchial asthma an increased incidence of these diseases

Recently Winer Beakey and Segal[201] made a clinicopathologic study of 16 autopsied cases from the files of the Mallory Institute of Pathology of the Boston City Hospital For purposes of analysis the 16 cases were divided into three groups on the basis of anatomical findings (1) those patients whose death occurred during an attack of bronchial asthma (2) those patients who died because of diseases which frequently accompany and may be related to bronchial asthma and (3) those patients who died because of intercurrent diseases

Of the 16 patients there were 13 in Group 1 who died during an attack of bronchial asthma Death during an attack of bronchial asthma is comparatively rare Unger[192] recently estimated that approximately 200 autopsy reports of deaths during an acute attack had been published up to that time and he discussed the reasons for the paucity of such reports The present series adds 13 cases The pathological findings of these cases where death occurred during an attack of bronchial asthma were essentially similar to those previously reported Thieme and Sheldon[188] stated that the pathological diagnosis of bronchial asthma can be made only when the majority of the following criteria are present (1) hyaline thickening of the basement membrane of medium sized bronchi (2) hypertrophy of the muscles of medium sized bronchi (3) mucus plugs in large and small bronchi (4) eosinophilic infiltration (5) saculation of the bronchi and (6) excessive production of mucus and widening of the mouths of the bronchial glands

Emphysema was uniformly present in these cases and in the great majority of reported cases Atelectasis occurred in only one case of this group Mucus plugs were present in each case The frequent occurrence of focal groups of neutrophils in both the lumen and wall indicates the presence of focal acute bronchitis superimposed on bronchial asthma The additional exudate may increase the degree of bronchial obstruction and may contribute to the development of bronchopneumonia and atelectasis

The status of the heart in bronchial asthma has been the subject of many previous studies [53, 107, 130, 150, 186, 192] Disagreement has been expressed as to the presence and importance of right ventricular strain and hypertrophy in uncomplicated bronchial asthma It has been demonstrated by means of cardiac catheterization[37] that an extreme degree of pulmonary emphysema or fibrosis might exist with little evidence of strain on the right side of the heart Another approach to the subject of pulmonary heart disease was made by Spain and Handler[180] who reviewed 60 cases of chronic cor pulmonale at necropsy They concluded that the primary cause of cor pulmonale was not obliteration of the pulmonary vascular bed fibrosis of the lungs or the influence of polycythemia but rather the result of the changed pressure relation within the alveoli producing an increased resistance to the flow of blood They felt that the term emphysema need not imply an associated pulmonary fibrosis There has also been recognition of the fact that asthmatics may have clinical signs and symptoms usually referable to cardiac failure but due to extracardiac factors [59]

Chronic bronchitis and emphysema may produce cough basal rales cyanosis dyspnea and orthopnea The calibre of the pulmonary capillaries is decreased in the presence of emphysema and signs of increased venous pressure may

result However in our group of patients with uncomplicated bronchial asthma there were four with definite hypertrophy of the right ventricle in the absence of hypertensive or valvular disease One patient had signs symptoms and anatomical evidence of right sided cardiac failure In the other three cor pulmonale was an incidental finding so far as the clinical course was concerned In other studies the finding of cor pulmonale in uncomplicated bronchial asthma has been variable

Thieme and Sheldon [36] reported seven cases of status asthmaticus each with central congestion of the liver In this study four cases had central congestion and atrophy of liver cells one case had central hemorrhagic necrosis Rich and co workers [5] have demonstrated that central congestion atrophy and even central hemorrhagic necrosis of the liver may result from anoxemia or anemia Blood counts were not available in two cases There was no significant anemia in the other cases Anatomically there was evidence of cardiac failure in only one case It is possible that the asphyxia of attacks of bronchial asthma may be related to the development of these hepatic changes

Particular attention was paid to lymphoid tissue and adrenal morphology in this group A possible relationship between bronchial asthma and the general adaptation syndrome was suggested in these cases by the observation of lymphoid changes resembling those described in the alarm reaction [5] Rather than one alarming stimulus shortly before death there were many repeated alarming stimuli occurring for days and even weeks preceding death Lymphoid and adrenal changes might be expected therefore to be variable The lymphoid changes which were seen in these cases have in the past been considered either toxic or inflammatory in origin It is possible that these changes may represent those of the alarm reaction

Findings on 16 patients in Group II showed that death was due to a pattern of diseases related to bronchial asthma the fundamental elements of which were chronic bronchitis and emphysema often associated with broncho pneumonia pulmonary fibrosis and cor pulmonale Cor pulmonale was more frequent in this group than in un complicated bronchial asthma Cardiac decompensation appears especially likely to develop in the presence of coronary artery disease or valvular disease superimposed on hypertrophy of the right ventricle

Death due to intercurrent disease was manifested in 17 patients (Group III) Emphysema was present in the ma jority of these cases There was evidence of chronic bron chitis in approximately 50 per cent of the cases Eosino phils were found in bronchial walls in one out of every four cases

In this group there were diagnostic anatomical findings of periarteritis nodosa rheumatic heart disease glomeru lonephritis amyloidosis and sarcoid Hypersensitivity has been suggested in the past as the pathogenesis for each of these diseases With the exception of the latter two dis eases these diseases have been included in the theories of the general adaptation syndrome

On the basis of these studies which are to be published in full Winer Beakey and Segal[20] concluded that alarm ing stimuli (histamine epinephrine hypoxia and emo tional stress) appear to be present during attacks of bron chial asthma that they are recurrent and that such stimuli may produce in man certain of the so called diseases of adaptation

5 Classification

There have been many attempts at classification of bronchial asthma One of the earliest by Salter[155] (1868)

clearly defines the various influences which may affect the bronchioles (intrinsic) and other influences mediated through the central nervous system by reflexes and otherwise Walker[200] in 1918 used the terms intrinsic and extrinsic and this classification has been the one most commonly taught Rackemann[140] has defined at various times working classifications of asthma based largely on two main groups the first beginning before the age of 30 years (extrinsic or allergic) and the other beginning after the age of 30 years (intrinsic—generally demonstrating no allergic factors) Cohen[52] has propounded an ingenious classification based largely on the present concept of immunochemistry His classification begins with three factors responsible for the H reaction in the bronchial mucosa namely the antigen antibody stimulus cholinergic stimulation and unknown stimuli The liberation of the H substance then acts to produce the asthmatic paroxysms in any of his three main groups extrinsic intrinsic and combined extrinsic and intrinsic

Most allergists employ the last three main groups as the basis for classification The patient with extrinsic asthma is generally defined as one under 30 years of age who demonstrates specific allergic sensitivity by history environmental control or by skin or serological tests His attacks are usually acute and (often) seasonal in character with complete freedom clinically between attacks Specific allergic therapy generally brings gratifying results Complications are few and longevity is not affected The intrinsic patient is generally over the age of 30 The causative factor appears to arise within the patient rather than in his environment Specific allergens are usually not demonstrable and the family history for allergy is usually negative Evidence of sino-bronchial disease and structural emphysema appears more commonly in patients of this

CHAPTER II

THE ALLERGIC CONCEPT AND MANAGEMENT OF BRONCHIAL ASTHMA

1 The Allergic State

THE term allergy implies a state of inherited hyper sensitivity to a foreign substance usually protein in na ture The hereditary factor in asthma appears to be a tendency to any type of allergy The allergic response is the important basic mechanism in the causation of asthma The specific response follows the antigen (allergen) anti body union The antigen antibody reaction causes the sensitized cells in the shock organ to which the antibody is bound to release a toxic substance Most investigators believe that an H (histamine like substance) C (cho line like substance) or X (an unknown substance) is released following the contact of the allergen with sensi tized cells of the bronchioles or that the action of hista mine is mediated by acetylcholine liberated following the stimulation of parasympathetic nerves It is the reaction to this common substance that accounts for the allergic response which is characterized by a marked local reaction of an inflammatory type involving particularly the mucosa of the bronchioles (the sensitized cells) This reaction is associated with marked capillary dilatation increase in the permeability of the capillaries increase in the protein content of the intercellular fluid engorgement of the lymphatic and blood capillaries increase in the lymph flow accumulation of inflammatory cells especially eosino phils and an accumulation of mucus secretion within the lumina of the bronchioles

In recent years significant advances have been made in our understanding of the immunological and physiological mechanisms involved and in the management of this disorder which raises so much havoc with the patient and his family. Specific antigen antibody reactions are characteristic of experimental allergy since serum antibodies can be definitely demonstrated and the specific sensitivity may be passively transferred to normal animals. In patients with allergic asthma although the specific sensitivity may be passively transferred (Prausnitz Kustner method) the amount of serum antibody (referred to as reagin) may be so diluted in the total body fluids as to become inadequate for *in vitro* detection [139] Cooke[34] and Loveless[112] have demonstrated that reagin a thermolabile antibody is found *only in the serum of naturally allergic individuals*. Reagin can be passively transferred to normal subjects but its formation cannot be induced by immunizing normal individuals with pollen. This antibody is closely bound to the "sensitized" cells of the skin and mucous membranes and reacts on contact with the antigen e.g. ragweed causing these cells to liberate the toxic substance which then accounts for the local reaction (hive) in the bronchioles. Thus when a subject who has inherited the capacity for developing reagin (the sensitizing antibody) in his bronchial mucous membranes inhales ragweed pollen the antigen antibody reaction occurs and asthma develops.

There is an inverse relationship between the amounts of antigen and reagin necessary for the production of an attack. In addition to reagin the omnipresent thermolabile sensitizing antibody these same subjects may develop another type of antibody which is thermostable has no cellular affinity and serves in a more protective capacity. The latter is a blocking or neutralizing antibody (artificially produced) whose function is to bind or neutralize

the specific antigen and prevent its interaction with the troublesome reagin This antibody is found in *both normal and allergic subjects* following pollen immunization However it cannot be demonstrated by passive transfer tests in normal individuals Unfortunately not all types of bronchial asthma can be explained on this specific immunological basis

2 The Immuno Chemical Approach to the Allergic State

The immuno chemical treatment of bronchial asthma should be directed toward (1) lowering the amount of reagin or making it less capable of sensitizing the cells of the shock organ (2) producing enough thermostable antibody to block and neutralize the effects of the specific antigen and thus *increase the tolerance for the specific* antigen and (3) neutralizing and protecting against the effects of the toxic H C or X substance ultimately responsible for the attack

Unfortunately these theoretical aims although very desirable are not often obtainable There appears to be *no satisfactory method for producing quantitative* reduction of or hyposensitization against the effects of reagin Allergic cleanliness and environmental changes can reduce the hazard of contact with the causitive allergen After hyposensitization by injections with a specific allergen formation of both the thermolabile sensitizing reagin and the thermostable antibody are stimulated With successful treatment sufficiently high titres of thermostable antibodies may be developed to combine with the antigen and thus prevent its union with the reagin There are great individual variations in ability to form thermostable antibodies Many allergists believe that the successful inhibition of the allergic response which the allergen

would otherwise initiate may depend upon the production of sufficient thermostable antibodies to act as blocking and neutralizing bodies Unfortunately as Alexander[5] has pointed out the mechanism by which clinical improvement occurs following specific pollen therapy remains unknown because of the lack of correlation between the titre of thermostable antibodies and the degree of improvement Furthermore Cooke[54,55] has called attention to the fact that there are several different and clinically active antigens in pollen extract with a blocking antibody specific for each This may explain further the difficulty in correlating clinical immunity with serologic determination of serum antibody

Finally in addition to the difficulties that arise due to the complex nature of antigens the need for more sensitive immuno-chemical methods for determining antibody *in vitro* has been called to our attention by Kabat[103,104] The immuno-chemical approach to the management of the asthmatic is limited because of these difficulties

The allergens may be classified into four main groups ingestants injectants inhalants and contactants Among the most common offenders (allergens) are pollens (chiefly trees grasses and weeds) animal and poultry danders and feathers molds and other fungi cosmetics (orris root rice powder and karaya gum) insect sprays (pyrethrum) foods and dermal contacts A searching history may reveal other concomitant allergic reactions such as infantile eczema urticaria non seasonal vasomotor rhinitis contact sensitivities (particularly drugs and sera) new household objects (bedding furniture etc) pets fur occupational skin and inhalatory contacts Still other factors may include fatigue exertion cold heat[111] respiratory tract infection non specific pulmonary irritants (dust fumes smoke and odors) and psychosomatic factors all of which

may assume variable degrees of importance when initiating or participating in such a reaction

Every attempt should be made to determine the responsible antigens A search for correlation of the attack to season and environment may reveal that the attacks occur in the spring and summer coincident with the peak of the three pollen seasons (trees grasses and weeds) in the winter with the prevalance of upper respiratory infections in the fall and winter due to house dust molds or other fungi related and coincident with heating of homes (boxed in radiators and exposed piping systems) and during any season with marked frequency of barometric and humidity changes

Food allergens due to inhalation or ingestion may cause bronchial asthma The inhalatory mechanism may be observed in millers or bakers but on the whole is seldom encountered The gastro intestinal route is more common Any food may act as an allergen The major food allergens generally produce prompt reactions The minor food allergens on the other hand produce delayed reactions Eating a single allergenic food may cause an explosion of allergic manifestations that may last one to two weeks The incidence of allergic response is generally related to the frequency of ingestion The food allergens are absorbed into the blood stream and pass to the sensitized cells of the shock organs in the nose bronchi or bronchioles thus producing an allergic rhinitis bronchitis or bronchial asthma Allergic bronchitis may or may not be associated with bronchial asthma It may be associated with an allergic rhinitis or follow an upper respiratory tract infection More commonly however it occurs without an upper respiratory tract infection

In discussing food sensitivity in asthmatic children Hill [2] stated that about 20 per cent of positive scratch

tests to foods are of etiologic significance Furthermore he pointed out the mother usually knows what food produces asthma and has omitted it before skin tests are done Nevertheless routine procedure should include a searching history or skin testing for all possible offending allergens Such tests however are not infallible and therefore should not be used as definite guides for diet control

When the offending foods can be definitely determined their omission from the diet should bring freedom from attack The next step should be to determine the patient s tolerance for the indicated allergen The eliminated foods may be taken one at a time on successive days and any change in symptoms noted Oral hyposensitization may then be attempted by introducing the food (corn wheat fish chocolate milk or eggs etc) in greatly diluted and small amounts and then gradually increasing the concentration and amount daily until the whole food can be taken When the offender is not known trial elimination diets [32] or other modifications may be resorted to As a first step milk beef broth or gruel may be given alone for two or three days If improvement follows additional foods may be added until the offender is detected Randolph [4] determined what he calls the base of sensitivity before recommending the type and plan of diet to be followed Generally if no relief is obtained within a period of seven to 10 days foods are not likely offenders

If a detailed history is inconclusive skin patch scratch and intradermal testing should be resorted to Unfortunately these procedures are time-consuming costly and generally disappointing Many substances with markedly positive skin reactions produce no asthma while at times substances with negative skin reactions produce asthma Furthermore these tests vary from time to time and new allergic sensitivities may be acquired Harmful and un

warranted restrictions despite critical interpretation of skin tests have been prescribed too frequently Removal of the offending allergen and intensive specific hyposensitization should be promptly instituted in all cases whenever possible It has been our custom to routinely advise perennial non specific hyposensitization with house dust extract and stock mixed bacterial vaccine or autogenous vaccine for patients with negative skin tests in whom a history of sensitivity to dust or upper respiratory infections can be elicited

Successful preventive therapy depends upon the determination of the causative allergens These should be removed from the patient s environment (allergic cleanliness) and intensive effort should be made to defend (hyposensitize) him against these allergens Further therapy should be directed towards removing the contributory factors *Because search for the responsible agents is difficult and often completely unsuccessful, emphasis on the allergic approach to management should not exclude physiologic therapy*

3 Drug Tolerance

There are certain general considerations that one should understand when employing drugs in the management of the asthmatic patient The incidence of intolerance toxic effects or true drug allergy following innocuous doses of drugs is considerably higher in asthmatics than in normal subjects Simple chemical substances are not of themselves perfect allergens but they can acquire specific allergenic activity when joined to proteins or certain complex molecules The distinction between allergic and toxic (pharmacologic) reactions is often difficult Furthermore sensitization may occur following the second administration of a drug after an interval of one to four weeks This is

particularly true of pontocaine[155] and many of the serious reactions and deaths observed have occurred with second usage at time of repeated bronchoscopy or bronchography A careful history of previous drug reactions should be sought for in asthmatic patients

The majority of patients in status asthmaticus soon become intolerant of most drugs as witnessed by the frequency of nausea abdominal pain vomiting restlessness itching of the skin and nose rashes and edema of the lips Other manifestations of drug sensitivity such as fever leucocytosis adenopathy and arthralgias occur less frequently No true sensitivity to adrenalin or aminophyllin has been reported however toxic reactions and refractoriness to both of these drugs may occur Furthermore deaths[1, 41, 156] have been reported attendant upon their use intravenously

Sherman[17] in a stimulating discussion of drug allergy classified the numerous drugs likely to act as excitants of asthma and rhinitis into proteins vegetable gums and crystalloids Among the protein drugs (therapeutic agents) producing these reactions are various foreign sera and toxoids virus and rickettsial vaccines from egg yolk liver insulin and pituitary extracts and papain (caroid) and pancreatin Vegetable gums employed in pharmaceutical preparations such as acacia karaya and tragacanth have caused asthma rhinitis and urticaria in susceptible individuals This may explain some of the reactions that have followed the use of some of the new antihistaminic tablet preparations

Crystalloid drugs such as quinine quinidine arsenicals phenolphthalein thiamine hydrochloride procaine pontocaine cocaine formalin sulfonamides penicillin and streptomycin (aerosols) intravenous sedatives (particularly sodium pentothal which may produce broncho-

warranted restrictions despite critical interpretation of skin tests have been prescribed too frequently Removal of the offending allergen and intensive specific hyposensitization should be promptly instituted in all cases when ever possible It has been our custom to routinely advise perennial non specific hyposensitization with house dust extract and stock mixed bacterial vaccine or autogenous vaccine for patients with negative skin tests in whom a history of sensitivity to dust or upper respiratory infections can be elicited

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The majority of patients in status asthmaticus soon become intolerant of most drugs, as witnessed by the frequency of nausea, abdominal pain, vomiting, restlessness, itching of the skin and nose, rashes and edema of the lips. Other manifestations of drug sensitivity, such as fever, leucocytosis, adenopathy and arthralgias, occur less frequently. No true sensitivity to adrenalin or aminophyllin has been reported; however, toxic reactions and refractoriness to both of these drugs may occur. Furthermore, deaths[7, 42, 120] have been reported attendant upon their use intravenously.

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Crystalloid drugs, such as quinine, quinidine, arsenicals, phenolphthalein, thiamine hydrochloride, procaine, pontocaine, cocaine, formalin, sulfonamides, penicillin and streptomycin (aerosols), intravenous sedatives (particularly sodium pentothal which may produce broncho-

spasm *per se* not on a sensitizing basis) and intravenous sclerosing agents should be used with caution in asthmatic subjects Accidental intravenous injections of drugs or allergenic agents[198,199] may also explain some instances of sudden collapse and death (anaphylactic reactions) Even idiosyncrasy to iodides bromides and chloral may be occasionally observed Other drugs particularly opium and morphine should be avoided As there is a high incidence of sensitivity to acetylsalicylic acid (aspirin) in asthmatics reactions to this drug are common and apt to be severe

Unfortunately skin tests except for patch tests in certain types of dermatitis are of no value for the detection of sensitivity to most crystalloid substances because of the absence of demonstrable circulating antibodies and furthermore they may be followed by severe constitutional reactions Presumably simple chemical compounds introduced into the body when combined with protein might act as haptenes (partial allergens) and determine the specificity of antibody reactions There is little evidence that the natural drug itself can produce allergy without this combination On the other hand skin tests and antibody determinations may be of value in the diagnosis of allergy to protein drugs and vegetable gums The degree of specificity and the duration of sensitivity to drugs vary greatly Drugs likely to produce sensitivity should be avoided in asthmatic subjects Trial dosage by the sublingual or oral route should be resorted to when doubtful Inhalatory or other parenteral routes should not be employed in such instances or serious reactions may follow

CHAPTER III

PROTECTION STUDIES*

THE clinical evaluation of drugs employed in the management of bronchospasm is extremely difficult and at best inaccurate In mild and transient episodes agents of weak or doubtful potency may give relief in status asthmaticus the desperate need for immediate relief does not allow controlled observation of the action of single agents In view of these difficulties a method of producing dyspnea and bronchospasm at will in sensitive subjects is employed

The search for a suitable bronchospastic substance active in the protean manifestations of allergy and anaphylaxis in animals and man has involved many investigators and countless studies In these varying and conflicting reports two substances (histamine and acetylcholine) have often been considered possible chemical mediators of allergic phenomenon Both of these substances are capable of producing dyspnea and bronchospasm in asthmatic subjects[6, 64, 67, 6, 187, 194, 195] and may be used in the evaluation of drugs capable of protecting against these effects[67, 69] With this technique a method of human assay of the relative value of new and accepted therapeutic agents for the relief of bronchial asthma has been evolved[63, 65, 169, 194, 195] By means of this technique we hope an approach may be made to the fundamental problem of the pathogenesis of bronchial asthma and thus to its management on a rational basis

* These studies were carried out in the Department of Inhalational Therapy of the Boston City Hospital supported in part through a grant from the United States Public Health Service I am indebted to the members of this department including former research fellows Drs J F Beakey and H R bitsky and my associates Drs F Bresnick and L. Levinson

1 Laboratory Methods for Producing Dyspnea and Bronchospasm

The effect of intravenous administration of histamine (Histamine diphosphate solution (Abbott) each cc represents 0 1 mgm of histamine base) or acetyl beta methylcholine (Mecholyl chloride solution (Merck) each cc represents 1 0 mgm) begins fifteen or twenty seconds after its administration The first effect is that of a disagreeable metallic taste thus assuring one of the intravenous administration accompanied or followed by the onset of a series of sensations related to vasodilatation and other compensatory cardiovascular phenomena These responses reach their maximum in approximately 30 to 60 seconds and consist of headache flushing palpitation and giddiness Administration of acetyl beta methylcholine often produced salivation lacrimation and a sense of substernal constriction but headache was not noted Serial determinations of the vital capacity after the administration of either of these agents revealed that the maximum diminution in vital capacity occurs approximately 30 seconds after the intravenous administration of the bronchospastic substance This drop was determined with stop watch timing by having the patient perform vital capacities at specified intervals after injection The most satisfactory intervals were found to be 30 seconds and then one two three and five minutes We have repeatedly shown that a patient is capable of performing vital capacities at 30 second intervals for several minutes without appreciable change As previously noted the maximum drop in vital capacity is almost invariably seen 30 seconds after injection Figure 3 depicts a typical response to the intravenous injection of a bronchospastic agent The vital capacity usually returns to normal in one to five minutes frequently it returns to levels somewhat higher than the original (rebound phenomenon)

After pre treatment of the experimental subject with a protecting agent the return of the vital capacity to the resting level following injection of the bronchospastic substance was usually more rapid

New patients generally first received intramuscular

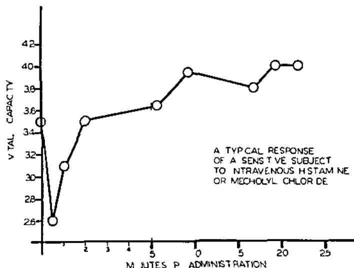


FIGURE 3

injections of 0 06 mgm of histamine or 0 1 mgm of mecholyl intramuscularly as test doses in order to detect any abnormal sensitivity no such instance was demonstrated The intravenous doses of histamine usually ranged from 0 01 to 0 01 mgm However two subjects reacted consistently to 0 005 mgm and one subject to 0 002 mgm The highest dose used in a protection study has been 0 06 mgm although greater amounts have been administered during the course of our investigations In general a dose of mecholyl sufficient to produce a significant drop in vital capacity was attended by much less

severe side effects than an equally effective dose of histamine The doses of mecholyl chloride administered intravenously usually ranged from 0 05 mgm to 0 4 mgm Sometimes the severity of the side reactions produced by histamine necessitated discontinuing the experiment before a dose capable of producing a decrease of the vital capacity could be given Side reactions to mecholyl were much better tolerated The most prominent symptom from overdoses of histamine usually was incapacitating headache However excessive doses of mecholyl produced more alarming effects Approximately 25 seconds after such an injection one patient seemed to lose consciousness A vacant stare appeared followed by momentary cessation of respiration and clonic movements of the arms and legs The entire reaction lasted only 10 to 15 seconds A solution of atropine sulfate was always kept ready in a syringe for immediate intravenous administration but no reaction long enough to warrant its use occurred Patients later described such reactions as going numb all over with a sense of constriction in the chest and transitory inability to move the limbs The clinical appearance of these reactions suggests transitory asystole

Administration of bronchospastic agents and of therapeutic substances by aerosols has been employed extensively In all instances we have made use of aerosols produced with the standard Vaponefrin nebulizer For uniformity a standardized technique for aerosol administration was devised The nebulizer was held by the experimenter with its outlet orifice close to the patient s open mouth The experimenter slowly counted aloud and at three the nebulizer bulb was squeezed with maximal force as the patient simultaneously made the deepest and most rapid inspiration possible following which he held his breath in inspiration for four or five seconds

The procedure was repeated at precisely ten second intervals until the desired number of inhalations (generally six) had been given. The stop-watch was then immediately reset; further time intervals were then calculated from the end of the last inhalation.

In contrast to the sequence of events following intravenous administration of histamine and of mecholyl, the

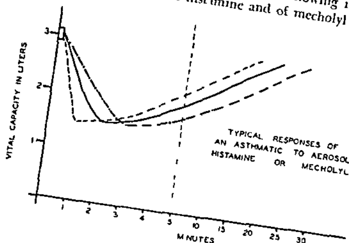


FIGURE 4

effect of these agents administered by the aerosol route is slower both in onset and in recovery. The maximal drop in vital capacity usually occurred one or two minutes after the last inhalation; in occasional instances it did not take place until three minutes thereafter. Recovery was usually complete within eight to ten minutes. A typical response of a sensitive subject to an aerosol of a bronchospastic agent is depicted in Figure 4. We have not observed the rebound phenomenon following the administration of histamine or of mecholyl by the aerosol route. Many patients describe mecholyl induced dyspnea

and bronchospasm as being more like their asthmatic paroxysms than histamine induced dyspnea and broncho spasm Side reactions have been infrequent when bronchospastic agents were administered in this way in contrast to their almost invariable occurrence to some degree after intravenous injection Those side effects which did occur were similar to the reactions already described but much less severe

2 Laboratory Evaluation of Therapeutic Agents (Protection Studies)

A protection study consists of determining the effect of a bronchospastic agent on vital capacity before and at varying intervals after administration of the drug under investigation (protecting drug) The resultant decreases in vital capacity are compared to the control drop Protection is demonstrated when administration of a bronchospastic agent causes either no drop in vital capacity or a drop distinctly less than the control amount Protection is lost when the decrease is once again equal to the control drop

A typical protection study was begun with a rest period of fifteen to twenty minutes the patient sat quietly and all constricting clothing was loosened The vital capacity was determined repeatedly until several trials were within plus or minus 100 cc The dose of bronchospastic agent required to produce a significant control drop in vital capacity was then determined either by aerosol or intravenous route Such a significant drop was usually 1 to 2 liters although sometimes it was necessary to accept slightly smaller decreases in those patients whose basal vital capacities were as low as 2 liters initially In this determination gradually increasing amounts of bronchospastic agent were administered every 20 to 30 minutes until a desirable decrease in vital capacity was obtained

In the case of intravenous histamine the increments were 0 005 or 0 01 mgm and in the case of mecholyl 0 05 or 0 1 mgm

After the control drop for the day was established and verified at least once the protecting drug was administered Following this vital capacities were again determined and followed by repeated administration of the bronchospastic agent at intervals of not less than 20 minutes Before each successive injection of the bronchospastic agent three to five vital capacities were obtained at intervals of one to two minutes in order to reaffirm the basal vital capacity from which the amount of the drop was to be calculated The new basal vital capacities were sometimes several hundred cc higher than the original basal readings this may have been due to the previously mentioned rebound phenomenon or to the therapeutic effect of the protecting agent or perhaps to the bronchodilating effect of repeated forced expirations (positive pressure therapy) *per se* The decrease in vital capacity when the bronchospastic agent was readministered was computed from this higher level which was frequently maintained for a considerable period of time Consequently when protection was finally lost i e when the decrease was equal to the control drop the point to which the vital capacity fell might still have been higher than even the original basal determinations The loss of protection was usually verified by at least one further dose of histamine or mecholyl

The sensitivity of the tracheobronchial tree to either of these substances varied in most subjects from day to day It was minimal during asthma free intervals and maximal during periods of active bronchospasm Sensitivity did not usually vary within one day and thus did not affect the course of any one protection study in the vast majority of

cases In a few instances a small dose of histamine or mecholyl appeared to potentiate the bronchospasm already present over and above its usual effect particularly in subjects with seasonal bronchial asthma studied during the height of the pollen season In such cases the vital capacity would fail to rise again over a considerable period of time or it even would continue to decrease Studies on subjects who may have been demonstrating mild bronchospasm on whom an adequate control drop in vital capacity could be obtained were as satisfactory as studies performed during periods of relative freedom from clinical asthma

Serial increases in the dose of the bronchospastic agent caused increasing drops in vital capacity which were not always in proportion to the increment in dose No cumulative effect was noted when the dose that caused a measurable decrease in vital capacity was repeated several times every twenty to thirty minutes Repetition of the same dose several times during a seven hour period showed that a refractory state of the tracheobronchial tree did not develop during the course of studies carried out for this length of time

Vital capacity determinations were sometimes invalidated by cough due to the stimulus created by forced expiration or by the bronchospastic agent itself If this effect were so marked as to preclude accurate consistent determinations the test was discontinued It was possible however to carry out adequate protection studies on some subjects in whom a bronchitic element was present Such patients often experienced a marked decrease in cough and sputum after the protection study was begun Once protection was established *spacing of basal readings, so* as not to excite the cough reflex was no longer necessary Another interesting observation in such patients was the

increase in vital capacity and decrease in cough that frequently occurred during the course of obtaining the basal readings. Apparently the act of forced expiration into the apparatus produced a slight positive pressure which was exerted backwards into the tracheobronchial tree as an internally distending force. Consequently the vital capacity often reached a figure much higher than the determinations recorded when the subject first arrived at the laboratory. Care had to be taken that studies were not begun until the vital capacity had been maintained consistently over several recordings.

Data denoting the degree of protection afforded by a given protecting agent again a bronchospastic drug have been derived from these experiments. *We have noted and emphasized that any one protection study in a single individual may have little general applicability.* We have attempted therefore to establish an algebraic equation by which the degree of protection could be expressed in terms applicable to many subjects so that the data might be subjected to some degree of statistical analysis. The decrease in vital capacity produced by a given dose of histamine or of mecholyl varied greatly from individual to individual but remained constant in the same individual for the period of one protection study. During a period of protection the decrease in vital capacity produced by the same dose of bronchospastic agent will by definition be less than the control drop. We have considered the percentage difference between these two values to be a measure of protection

$$P = \frac{C - T \times 100}{C}$$

where P is the degree of protection in per cent, 100 per cent indicating absence of any decrease in vital capacity

after the administration of histamine or of mecholyl C is the control drop in vital capacity produced by the introduction of the same quantity of the bronchospastic agent before administration of the protecting drug and E represents the decrease similarly produced at any given time after the protecting drug has been administered

Accurate evaluation of protection demands that the control drop in vital capacity exceed 1000 cc We prefer to work within the range of 1200 to 1500 cc When for example 1200 cc is achieved as the control drop a later decrease of 800 cc would appear to indicate a protection of 33⅓ per cent—

$$\frac{1200 - 800 \times 100}{1200} = 33\tfrac{1}{3} \text{ per cent}$$

However variations of plus or minus 100 cc both in the basal vital capacity and in the determination thirty seconds after an intravenous injection of the broncho spastic agent may produce in any individual instance a total difference of as much as 200 cc in the drop An additional variation of 200 cc can be accounted for by virtue of the fact that the bronchospastic agent cannot be relied upon to produce precisely the same effect every time *The total range of variation then might be as much as 400 cc*

If 600 to 800 cc were accepted as a control decrease in vital capacity a later drop (after administration of a protecting drug) of only 200 to 400 cc might be considered to demonstrate considerable protection Obviously how ever this would be open to serious error *Therefore, we have always attempted to attain control drops of 1200 to 1500 cc and consider protection significant only when it is 40 per cent or more*

This transformation of data from vital capacity readings

in cubic centimeters to percentage figures eliminates the dose of the bronchospastic agent from consideration as a variable factor It also facilitates the statistical presentation of such data obtained from experiments on different subjects into one curve of increased statistical probability Such a graph representing the massed data from four

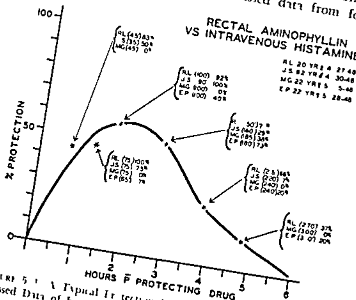


FIGURE 5 — A Typical Protection Study Curve Obtained from the Massed Data of Four Protection Studies Derived from a Total of Thirty Individual Doses of a Bronchospastic Agent

protection studies derived from a total of thirty individual doses of a bronchospastic agent is presented in Figure 5

3 Protection Studies with Anticholinergic Drugs (Atropine Scopolamine and Bellafoline)

It has been the opinion of many investigators that bronchial asthma may represent an imbalance of the

autonomic nervous system If bronchial asthma were predominantly due to an over activity of the cholinergic apparatus then it should respond most satisfactorily to treatment with drugs which block the action of these nerves The classical agents which inhibit the effects of postganglionic nerve impulses are the alkaloids of the belladonna group This group of alkaloids consists in the main of two hyoscine and hyoscyamine We[33] have limited our protection studies to the use of the two commonly available alkaloids atropine (racemic hyoscyamine) and scopolamine (levohyoscine Hoffman LaRoche) In order to compare the effects of hyoscine and hyoscyamine directly we have also made use of a preparation of mixed belladonna alkaloids which has been assayed in terms of levohyoscyamine only (Bellafoline Sandoz) These parasympatholytic agents atropine scopolamine and Bellafoline have demonstrated excellent anticholinergic protection in our laboratory (Table 2)

Atropine a naturally occurring racemic belladonna alkaloid is composed of equal parts of the optical isomers of hyoscyamine Since the dextro hyoscyamine has a very weak peripheral action the potency of atropine is due to its levohyoscyamine fraction Atropine has consistently demonstrated greater ability to inhibit mecholyl induced bronchospasm than histamine induced bronchospasm Scopolamine (levo rotatory hyoscine) also occurs naturally It demonstrated marked anticholinergic properties when administered subcutaneously (0 3 mgm) However Bellafoline a synthetic preparation believed to be composed of total levo rotatory alkaloids of belladonna manifested the most marked anticholinergic action Since Bellafoline has little or none of the inactive dextro hyoscyamine which is present in atropine its greater potency is easily explained Oral scopolamine and Bellafoline show excellent protection however their reaction is slower

[illegible]	HISTAMINE I.V.				MECHOLYL I.V.				MECHOLYL AEROSOL			
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

TABLE 9 3

Aerosols of scopolamine and Bellafoline (a therapeutic dose represented by six inhalations of the solution administered in one minute) demonstrated excellent but relatively short lived protection against intravenous and aerosolized mecholyl. Considering the very dilute solution employed (0.06 and 0.05 per cent respectively) the degree of protection is truly remarkable. *The protective action against bronchospastic aerosols was greater than against intravenous bronchospastics.*

In many experiments involving the use of these parasympatholytic alkaloids a striking sedative action has been noted. In some cases the subcutaneous administration of 0.3 mgm. of scopolamine has resulted in deep drowsiness or sleep lasting for as long as two or three hours. Similar reactions have been noted with Bellafoline. Sedation was less evident following atropine, which was to be expected.

It may be perceived from the data presented in Table 2 that in each case a protecting agent reaching its site of action via the blood stream seems more efficacious in combating the effects of a bronchospastic agent administered by the same route. A protecting drug given as an aerosol is more potent against bronchospastic aerosols than against bronchospastic agents given by vein. This finding is difficult to interpret. One may speculate that aerosols reach the motor end plates of the bronchial musculature by direct diffusion, thus differing from the path taken by substances reaching the lung via the pulmonary circulation. Perhaps aerosols and blood borne medications do not exert their action entirely in the same effector area; the protecting agent given by one route covers all the effectors which may be reached by a bronchospastic drug later administered by the same route, but leaves uncovered some other effectors which still remain sensitive to bronchospastic agents administered

via a different route This concept may have wider applicability to the rationale of treatment of bronchial asthma particularly in resistant cases and may indicate the advisability of simultaneous aerosol and intravenous medication This reasoning is somewhat similar to what we have demonstrated as fact in a study of the pharmacodynamics of pulmonary absorption of penicillin in suppurative diseases of the lung[36] The same hypothesis may cast some light on the variations in response to therapy of patients with extrinsic (inhalant) and intrinsic asthma

Clinically it is well kown that atropine is not an effective bronchodilator and that it is almost useless in the treatment of bronchial asthma In addition its drying action on the mucous membranes of the tracheobronchial tree leads to further inspissation of already semi solid mucus plugs This makes coughing and expulsion of these plugs an even more difficult task for the asthmatic and renders him more liable to recurrent bronchospasm and to obstructive atelectasis Despite the excellent ability of these medications to combat the effects of injected mecholyl in the laboratory atropine scopolamine or Bellafoline will serve a very limited role in the therapeutic armamentarium of the pneumatologist in his attempt to counteract the bronchospasm of bronchial asthma Scopolamine has a stronger action than atropine on the secretory glands and has a far more marked central sedative effect the latter effect is highly desirable in many cases The wet sweating hypotensive asthmatic who may be exhibiting a systemic picture of parasympathetic stimulation (pathological vagotonia) is almost completely resistant to ordinary methods of treatment It is possible that hyoscine hyoscyamine or a derivative may exhibit sufficient sedative as well as bronchospasmolytic properties in such asthmatics that its use might be indicated in spite

of its drying action. We hope that the pharmacologist will be able to devise a compound which will retain the *sedative action and the usual anticholinergic* properties of the parent drug but with less local effect on the bronchial mucosa.

The results of these experiments demonstrate that the alkaloids of the belladonna group are, as could have been predicted, dramatic inhibiting or protecting agents against the deleterious bronchospastic effects of injected or aerosolized mecholyl and that they have little or no effect on the bronchospasm produced by the administration of histamine. Although these results may have little clinical value, they offer some theoretical significance. In bronchial asthma we are dealing with a disease of unknown pathogenesis. It has been suggested that in the asthmatic acetylcholine acts upon a sensitive end organ, the bronchial musculature and submucosa, to produce bronchial edema (the bronchial hive), bronchial muscular constriction and thereby bronchospasm, all of which may be additive and result in a paroxysm of asthma. We have been able to show conclusively that injected mecholyl has similar effects but that these effects may be completely inhibited by pre-treatment with an alkaloid of the belladonna group. On the other hand, these alkaloids alone are ineffective in the treatment of clinical asthma.

These observations are essentially similar to those of Dale and Gaddum[64] who studied the *contracture which* occurs in denervated voluntary muscle when the parasympathetic vasomotor fibers supplying the vessels within the muscle are stimulated. This contracture occurs beyond doubt by the diffusion of acetylcholine liberated in the walls of the blood vessels in response to vasomotor impulses into the neighboring muscle tissue. *However, the* contracture was not prevented by atropine. Dale and

Gaddum propose that in this and similar situations the liberation of acetylcholine occurs in an anatomical area so close to the effector tissue that atropine in unable to exert its usual inhibitory effect Such a mechanism may also be present in the bronchioles

4 Protection Studies with Sympathomimetic Amine Aerosols (Epinephrine, Vaponefrin Isuprel and Neosynephrin)

Because of the widespread clinical interest in the use of aerosols of various sympathomimetic amines for the management of bronchial asthma we undertook a comparative study of the protective abilities of aerosols of epinephrine (1 100) neosynephrin (1 100) Vaponefrin and Isuprel (1 200 and 1 100) against the effects of intravenous histamine and mecholyl induced dyspnea and bronchospasm in asthmatic subjects[164] The aerosols were produced by hand bulb nebulization with the Vaponefrin nebulizer The dosage of each therapeutic or protecting agent consisted of six deep inhalations of the specific aerosol The protection afforded (immediate protection

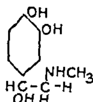
	BRONCHOCONSTRICTING AGENT			
	HISTAMINE IV		MECHOLYL IV	
PROTECTING AEROSOL	IMMEDIATE PROTECTION PERCENT	DURATION OF SIGNIFICANT PROTECTION [illegible] MINUTES	IMMEDIATE PROTECTION PERCENT	DURATION OF SIGNIFICANT PROTECTION [illegible] MINUTES
EPINEPHRINE [illegible]	75	28	56	8
VAPONEFRIN [illegible]	93	27	74	8
NEOSYNEPHRIN [illegible]	52	6	32	0
ISUPREL [illegible]	70	22	69	42
[illegible]	98	62	9	8

TABLE 3[164] Comparative Protective Value of Sympathomimetic Aerosols against IV Histamine and Mecholyl Induced Dyspnea and Bronchospasm in Asthmatic Patients.

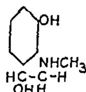
in per cent and the duration of significant protection in minutes) appears in Table 3

Epinephrine, the hormone of the adrenal medulla, is *the parent substance of the sympathomimetic amines*[124] It is a secondary amine and basically an ethylamine

EPINEPHRINE



NEOSYNEPHRIN



ISUPREL

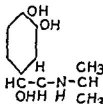


FIGURE 6[41] The Structural Formulae of Three Sympathomimetic Amines Under Discussion

derivative Gunn[95] and later Graham and Gurd[8] separated those sympathomimetic amines which are ethylamine *derivatives from a second group derived from isopropylamine* (ephedrine and its congeners) All the substances under discussion at this time are ethylamines The structural *formulae of the three* compounds under discussion are presented in Figure 6

Chemically Isuprel differs from epinephrine only in *the substitution of an isopropyl radical for a methyl group*

in the aliphatic portion of the molecule Neosynephrin is even more similar to epinephrine structurally the only difference being the absence of the para hydroxyl group present in epinephrine As will be demonstrated with regard to the bronchi and as is well known so far as pressor activity is concerned[65] this alteration in the aromatic portion of the molecule produces greater variations in the pharmacological properties of the compound than do changes in the aliphatic chain Vaponefrin is chemically identical to epinephrine but epinephrine consists solely of the levorotatory isomer whereas Vaponefrin is a racemic mixture of both levo and dextro-rotatory isomers Since the dextro-rotatory epinephrine is less active pharmacologically than the levo rotatory isomer Vaponefrin may be expected to be less potent by weight of the dry material than epinephrine

Epinephrine hydrochloride 1 100 U S P—Six inhalations of the mist produced from a solution of epinephrine hydro chloride 1 100 by hand bulb nebulization with the Vaponefrin nebulizer provided excellent protection (75 per cent) against the bronchospastic effects of intravenous histamine The results were immediate (five to 10 minutes after ad ministration) however the degree of protection decreased fairly rapidly reaching the level of 10 per cent after 28 minutes In view of the numerous sources of error inherent in any technique of clinical assay we have proposed[171, 289] this 10 per cent level to be the minimum degree of protec tion which may be considered significant By contrast epinephrine 1 100 was less potent in counteracting the ef fects of intravenous mecholyl showing an immediate pro tection of 56 per cent which fell to 10 per cent at the end of 18 minutes These results and those presented below are presented in tabular form in Table 3

Vaponefrin (a 2 25 per cent solution of specially prepared

racemic epinephrine hydrochloride)—The chemical and pharmacological properties of Vaponefrin have been described by Munch, Gattone and Pratt[176] In acute toxicity tests on animals they found that, following injection, Vaponefrin was about two thirds as toxic as epinephrine In chronic inhalational studies on rabbits no toxic effects were observed following inhalation of up to 4000 inhalations of Vaponefrin Finally, the pressor potency of Vaponefrin base was found to be about two thirds the pressor potency of epinephrine base following intravenous injection in anesthetized cats, dogs and monkeys Richards, Barach and Cromwell[148] considered Vaponefrin clinically preferable to the official 1 100 solution of epinephrine hydrochloride This preparation has been extensively employed *by numerous investigators as a potent bronchodilator* aerosol[18 46 106 153 162]

The Vaponefrin preparation demonstrated greater protecting ability in these experiments than 1 100 epinephrine Against histamine, Vaponefrin displayed essentially complete immediate protection (93 per cent), with significant protection (10 per cent or higher) which persisted for 27 minutes Its protection against the effects of mecholyl induced bronchospasm was less marked than against histamine, demonstrating an immediate protection of 74 per cent, with significant protection persisting for 18 minutes Thus Vaponefrin surpasses epinephrine 1 100 in the completeness of immediate protection against both histamine and mecholyl Both Vaponefrin and epinephrine 1 100 protect more efficiently against histamine than against mecholyl

Neosynephrin 1 100—Neosynephrin 1 100 has often been used as a bronchodilator aerosol[22 46 145 160] Graeser[89] found it far inferior to epinephrine in the same concentration However, Richards, Barach and Cromwell[148] were able to

produce significant bronchodilation with neosynephrin 1 100 by their continuous inhalation technique It has a prolonged and marked local vasoconstrictor action after local application to the mucous membranes of the respiratory tract but it is a poor bronchodilator It may provide a more patent airway by virtue of its action as a bronchovasoconstrictor [27, 48, 145, 160] In our experiments[41, 169] its immediate protecting capacity against the effects of histamine was only 52 per cent, with significant levels being maintained for only 16 minutes No significant protecting action against the bronchospastic effects of mecholyl could be demonstrated

Isuprel (1 (3′,4′-dihydroxyphenyl) 2 isopropylaminoethanol hydrochloride—During the early years of this decade occasional reports from Europe mentioned an extremely potent bronchodilating agent known as Aleudrin [49, 68, 70] It was extremely efficacious in the treatment of clinical asthma and was rated superior to all other compounds tested in counteracting the dyspnea induced by aerosols of carbaminoylcholine In animal experiments Aleudrin was described as ten times more powerful than epinephrine This drug under the name of Isuprel was first introduced into the American literature in 1947 by Segal and Beakey[166, 167] who were not aware of its chemical identity with Aleudrin until their studies were nearly completed The pharmacological properties of Isuprel have been reported in detail by Marsh Pelletier and Ross[113] and by Lands Nash Dertinger Granger and McCarthy [109] The excitatory effects of epinephrine can be largely eliminated and the inhibitory effects enhanced by making substitution on the amino nitrogen in the epinephrine molecule To prepare Isuprel the chemists substituted an isopropyl group in place of the methyl group on the nitrogen This results in a compound with less excitatory

effects and more inhibitory actions than epinephrine (Fig 6)

Isuprel is ordinarily employed in a dilution of 1 200 a solution one-half as concentrated as that used with epinephrine and neosynephrin and approximately one fifth as concentrated as Vaponefrin This solution demonstrated 70 per cent immediate protection against the effects of histamine significant protection was maintained for 22 minutes Surprisingly it proved to be of greater protecting value against the effects of mecholyl 69 per cent immediate protection dropped quite slowly to 40 per cent at the end of 42 minutes Thus aerosols of Isuprel 1 200 demonstrated more prolonged and more intense protection against the effects of mecholyl than epinephrine Vaponefrin or neosynephrin aerosols but proved inferior as histamine antagonists to both epinephrine 1 100 and Vaponefrin

Aerosols of Isuprel 1 100 demonstrated complete immediate protection (98 per cent) against the effects of both histamine and mecholyl This protecting action gradually lessened and dropped to 40 per cent after 62 minutes in the case of histamine and after 81 minutes with mecholyl Isuprel 1 100 proved to be the most effective aerosol for protection against the effects of histamine and mecholyl in our laboratory It is unfortunate that this concentrated solution is too prone to produce disturbing side-effects for routine clinical use This is particularly true for the ambulatory patient [166 167]

These laboratory studies confirm our previous reports on the clinical management of bronchial asthma [160 161 18 166 67] Both Isuprel 1 200 and Vaponefrin are effective bronchodilator aerosols with powerful albeit short lived bronchospasmolytic properties Isuprel is the most powerful antagonist of acetylcholine Vaponefrin the most

potent against the effects of histamine Clinical experience with the two preparations reveals that either of the drugs may prove more satisfactory in any individual patient and that the comparative potency of the two preparations may vary from time to time in the same patient Patients may become refractory to either drug but loss of sensitivity to one is not associated with fastness to the other Both Isuprel 1 200 and Vaponefrin have valuable places in the armamentarium of the clinician treating bronchial asthma One must determine which is the drug of choice for each individual patient at any given time by careful observation and clinical trial Neosynephrin 1 100 an effective bronchovasoconstrictor with minimal antihistaminic properties has an advantage in that refractoriness is rarely observed It may be combined with any of the other amines to provide an effective solution for aerosolization

5 Protection Studies with Aminophyllin

Aminophyllin has been called the one two remedy in bronchial asthma [70] Aminophyllin shares with the sympathomimetic amines the ability to protect in the laboratory against the bronchospastic effects of *both* histamine and mecholyl Like them it is of great value in the clinical management of bronchospasm In comparison with the data obtained by similar examination of the protecting ability of various adrenergic agents against the dyspnea and bronchospasm produced by intravenous injections of histamine and mecholyl it is apparent that aminophyllin must exert its bronchospasmolytic action in a different manner The sympathomimetic amine aerosols in minute doses have a rapid intense protecting action against the bronchospastic effects of histamine (physiologic antagonism) whereas the effect of amino-

phyllin is milder and more prolonged and the dose employed is many times greater In dosage and in the time sequence of its protection aminophyllin approaches more closely the newer classical antihistaminic drugs (histaminolytic agents) data on which will be presented elsewhere in this book[170]

The protecting ability of aminophyllin administered by various routes against the dyspnea and bronchospasm produced by the administration of histamine and mecholyl by various routes is presented in Table 4 We have long been aware of the powerful bronchospasmolytic action of aminophyllin administered rectally in the management of patients with severe asthma This clinical impression is confirmed by these studies in which aminophyllin administered rectally exhibits a protecting action equal or similar to all other routes if the 45 to 60 minute absorption delay time is not objectionable Absorption after oral administration is slower and the period of significant protection shorter so that this route can have only limited value Intramuscular aminophyllin shows surprisingly poor protection which is not entirely unexpected from our clinical experience Were the pain usually attendant upon such an injection not already a sufficient deterrent to its clinical use the lack of significant protecting ability should make one hesitate to employ this route for the administration of aminophyllin It is our feeling that rectal aminophyllin affords the patient a potent means for relief of bronchospasm surpassed by the intravenous route only in speed of action The ease of self administration of rectal solution of aminophyllin is of course an even more important factor

Our inability to demonstrate adequate protection with aminophyllin aerosol is seemingly at variance with the clinical observations of Prigal[132, 133] who used much greater

BRONCHOCONSTRICTING AGENT

PROTECTING DRUG	HISTAMINE IV: LATENT PERIOD OF DEVELOPMENT OF 40% LEVEL (MIN)	HISTAMINE IV: PEAK LEVEL %	HISTAMINE IV: PEAK TIME P INJ (MIN)	HISTAMINE IV: DURATION OF SIGNIFICANT 40% PROTECTION (MIN)	MECHOLYL IV: LATENT PERIOD OF DEVELOPMENT OF 40% LEVEL (MIN)	MECHOLYL IV: PEAK LEVEL %	MECHOLYL IV: PEAK TIME P INJ (MIN)	MECHOLYL IV: DURATION OF SIGNIFICANT 40% PROTECTION (MIN)
[illegible]	0	65	IMMED.	130	—	37	IMMED.	0
[illegible]	—	38	50	0	—	38	90	0
[illegible]	45	38	120	150	55	45	105	90
[illegible]	105	45	130	50	130	42	135	20
[illegible]	—	12	75	0	—	12	15	0

COMPARATIVE PROTECTIVE VALUE OF AMINOPHYLLIN ADMINISTERED BY VARIOUS ROUTES AGAINST HISTAMINE AND MECHOLYL-INDUCED DYSPNEA AND BRONCHOSPASM IN ASTHMATIC SUBJECTS.

* AMINOPHYLLIN AEROSOL ALSO EXHIBITED NO SIGNIFICANT PROTECTION AGAINST THE EFFECTS OF HISTAMINE AND MECHOLYL AEROSOLS

TABLE 4[19]

phyllin is milder and more prolonged and the dose employed is many times greater In dosage and in the time sequence of its protection aminophyllin approaches more closely the newer classical antihistaminic drugs (histaminolytic agents) data on which will be presented elsewhere in this book.[170]

The protecting ability of aminophyllin administered by various routes against the dyspnea and bronchospasm produced by the administration of histamine and mecholyl by various routes is presented in Table 4 We have long been aware of the powerful bronchospasmolytic action of aminophyllin administered rectally in the management of patients with severe asthma This clinical impression is confirmed by these studies in which aminophyllin administered rectally exhibits a protecting action equal or similar to all other routes if the 45 to 60 minute absorption delay time is not objectionable Absorption after oral administration is slower and the period of significant protection shorter so that this route can have only limited value Intramuscular aminophyllin shows surprisingly poor protection which is not entirely unexpected from our clinical experience Were the pain usually attendant upon such an injection not already a sufficient deterrent to its clinical use the lack of significant protecting ability should make one hesitate to employ this route for the administration of aminophyllin It is our feeling that rectal aminophyllin affords the patient a potent means for relief of bronchospasm surpassed by the intravenous route only in speed of action The ease of self administration of rectal solution of aminophyllin is of course an even more important factor

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PROTECTING DRUG	BRONCHOCONSTRICTING AGENT: HISTAMINE IV — LATENT PERIOD OF DEVELOPMENT OF 40% LEVEL (MIN)	PEAK LEVEL %	PEAK TIME $\bar{P}$ INJ. (MIN)	DURATION OF SIGNIFICANT 40% PROTECTION (MIN)	MECHOLYL IV — LATENT PERIOD OF DEVELOPMENT OF 40% LEVEL (MIN)	PEAK LEVEL %	PEAK TIME $\bar{P}$ INJ. (MIN)	DURATION OF SIGNIFICANT 40% PROTECTION (MIN)
AMINOPHYLLIN 0.5 GM IN 20 CC IV	0	65	IMMED.	130	—	37	IMMED.	0
AMINOPHYLLIN 0.5 GM IN 2 CC IM	—	38	50	0	—	38	90	0
AMINOPHYLLIN 0.5 GM IN 20 CC H2O RECTALLY	45	58	120	150	55	45	105	90
AMINOPHYLLIN 0.4 GM (CT) ORAL	105	45	130	50	130	42	135	20
AMINOPHYLLIN * 0.5 GM IN C AEROSOL	—	12	75	0	—	12	15	0

COMPARATIVE PROTECTIVE VALUE OF AMINOPHYLLIN ADMINISTERED BY VARIOUS ROUTES AGAINST HISTAMINE AND MECHOLYL-INDUCED DYSPNEA AND BRONCHOSPASM IN ASTHMATIC SUBJECTS.

* AMINOPHYLLIN AEROSOL ALSO EXHIBITED NO SIGNIFICANT PROTECTION AGAINST THE EFFECTS OF HISTAMINE AND MECHOLYL AEROSOLS

TABLE 4[179]

doses of the drug vaporized by his steam vaporizer The difficulties attendant upon the use of this technique in the clinical management of asthmatic patients led us to try aminophyllin in the Vaponefrin nebulizer The results are described in Table 1 We have also been unable to demonstrate any significant improvement in the vital capacities of our asthmatic subjects following inhalation of 0 25 gm aminophyllin (1 0 cc) solution

6 Correlation of Laboratory and Clinical Data

We have employed by aerosol as well as by intravenous route histamine acetyl beta methylcholine and allergenic extracts as bronchospastic agents [111] With this human assay method we have investigated various classes of drugs including anticholinergic agents [83] adrenergic agents [41] aminophyllin by all possible routes [170] antihistaminic agents [54] Cytochrome C Khellin (Ammicardine) and a number of other miscellaneous drugs We have obtained statistically valuable data describing the degree of protection afforded by a given protecting agent against a bronchospastic drug Some of these observations have been presented At the present stage of our studies several correlations of this laboratory data with clinical observations seem noteworthy

We have demonstrated that anticholinergic drugs such as atropine scopolamine and Bellafoline are extremely effective against the dyspnea and bronchospasm produced by mecholyl but that they have no effect on that produced by histamine Conversly antihistaminic drugs (blocking agents) abolish almost completely the decrease in vital capacity following intravenous injections of histamine but most of these agents have no significant effects against mecholyl [154] Nevertheless both of these classes of substances have minimal bronchospasmolytic

properties and limited value in the clinical management of the asthmatic patient

Two drugs aminophyllin and epinephrine are very valuable in the management of the asthmatic Both are excellent bronchospasmolytic agents in the physiologic sense According to our laboratory and clinical data epinephrine is a good protecting agent against the bronchospastic effects of histamine and mecholyl and also works very well in clinical asthma Aminophyllin [170] on the other hand is a fair protecting agent against the bronchospastic effects of histamine but it is less efficient against the effects of mecholyl Hence aminophyllin because of its dual properties of being an antihistaminic and a bronchodilator drug is an excellent agent for the clinical management of the asthmatic patient when it is administered by different routes at various intervals of the patient's illness The efficacy of intravenous aminophyllin in the epinephrine fast state is of particular interest An examination of the structural formula of theophylline shows that it contains an imidazol ring and there by an imino grouping which may enhance it with antihistaminic potentialities albeit weak The epinephrine fast patient may release more histamine with accentuation of dyspnea and bronchospasm (histamine sympathin balance—see Chapters V and VI) Fundamentally the action of aminophyllin at this point may be similar to that of the antihistaminics (although to a lesser degree) namely to bind the cell receptor substance in place of histamine thus bringing relief to the competition of histamine sympathin on the smooth muscle and sway the seesaw to the epinephrine side [78 18 204 205]

We are cognizant that the spontaneous asthmatic paroxysm differs in many ways from the experimentally induced paroxysm of dyspnea and bronchospasm The

circulating chemical mediators in both types of asthma are probably the same The intracellular release of histamine (which occurs in spontaneous bronchial asthma) is not simulated in the laboratory Nevertheless this technique most closely approaches the asthmatic paroxysm under ideal laboratory conditions With these protection studies the physiologic and pharmacologic effects of the various therapeutic agents being studied should be distinguished True physiologic antagonism is demonstrated by the epinephrine preparations (bronchospasmolytic properties) against the effects of histamine wherein both drugs act on effector cells in opposite directions and the effect of one tends to neutralize that of the other [208] True pharmacologic antagonism is demonstrated by cholinolytic sympatholytic or histaminolytic agents (blocking properties) against the effects of acetylcholine sympathin and histamine respectively The cholinolytic and sympatholytic agents do not interfere with the release of the chemical mediators of parasympathetic and sympathetic stimulation but do prevent these mediators acetylcholine and sympathin respectively from reaching the receptor mechanisms of effector cells and exerting their characteristic action Similarly the histaminolytic agents (antihistaminics) do not prevent the release of histamine but rather prevent the histamine from reaching the receptor mechanism in the cell where the histamine exerts its characteristic effects [208]

The atropine group and the antihistaminic drugs are ideal blocking agents Their shortcomings as ideal antiasthmatic drugs may be appreciated however when one realizes that the site of histamine release following the antigen antibody reaction is probably intracellular This most likely also holds true with the liberation of acetylcholine by cholinergic nerve stimulation Thus the

circulating chemical mediators of experimental and spontaneous bronchial asthma can be blocked but the reactions which occur within the affected cells cannot be effectively blocked

The development of non toxic agents to prevent the intracellular release of histamine or acetylcholine release appears unlikely at present It would appear from our data that the combination of a good antihistaminic and a good anticholinergic drug with direct bronchospasmolytic properties (free of allergenic potentialities and possessing minimal toxicity) would be the most ideal therapeutic agent in bronchial asthma It should inhibit or neutralize the effects of histamine and acetylcholine and bring prompt relief from the asthmatic paroxysm It is not unlikely that the organic chemist will so shake up the structure of various benzene ring combinations without abolishing the activity of each moiety as to synthesize such a compound in the near future

CHAPTER IV

SEDATION

EVERY effort should be made to put the patient at complete mental and physical rest *Psychic trauma may* be an important trigger mechanism in initiating an acute attack or modifying intractable asthma It is best to avoid heavy sedation as the incidence of obstructive asphyxia and pulmonary edema is highest in the deeply sedated patient Therefore those agents which have a wide margin of safety should be used

1 The Barbiturates Chloral hydrate and Sodium bromide

The barbiturates like morphine depress the respiratory center until it is less sensitive to stimulation than normal *Phenobarbital orally in doses of 15 to 100 mgm may* produce adequate relaxation in the mildly dyspneic patient but barbiturates on the whole are disappointing Sodium pentothal as previously mentioned should be used with great caution It should not be administered during the asthmatic paroxysm Sodium phenobarbital may give better sedation than sodium amytal seconal or nembutal However any of these drugs may produce irrationality and excitability A dose of 0 1 to 0 2 gm of sodium phenobarbital may be given subcutaneously or in an intravenous infusion once or twice a day If the barbiturates or morphine must be used pre or post operatively it is advisable to administer supplementary oxygen As a general rule it is best to refrain from using morphine and aspirin in asthmatic subjects particularly post operatively

The combination of chloral hydrate and sodium bro-

mide is of particular value in the management of the patient in status asthmaticus This combination may be given rectally in doses of from 1 to 3 gm each and may be repeated at twelve hour intervals for several days without fear of serious respiratory depression Bromide intoxication and rash may follow prolonged usage When prolonged usage is necessary the former condition may be prevented by increasing the sodium chloride intake and thereby increasing bromine excretion

2 **Morphine Dihydro morphine hydrochloride (Dilaudid) and Meperidine (Demerol)**

Occasionally one sees very striking relief of dyspnea in the asthmatic patient with the initial use of morphine sulfate (8 to 10 mgm subcutaneously) I prefer to avoid the use of morphine in all asthmatic patients because with repeated doses serious sequelae may follow Such therapy has been decried for many reasons [1 8 19] On the whole morphine tends to depress the respiratory rate diminish the tidal volume and decrease the minute volume of respiration thus increasing the degree of hypoxia It also decreases the cough reflex prevents effective expectoration and thus may increase the tendency towards (segmental) atelectasis With repeated use the physiologic positive pressure within the tracheobronchial tree may be lost and pulmonary edema may follow At times morphine appears to produce additional nausea vomiting and bronchospasm Besides there is always the possibility of hypersensitivity and of addiction to the drug itself Finally death following morphine therapy to patients in status asthmaticus has been frequently reported and in most instances could be attributed to its use

Two of the three fatalities which occurred in the author s series of cases followed shortly after the repeated use of

small doses of morphine The house officers who attended these two middle aged patients described typical episodes of obstructive phenomena with markedly labored noisy respirations ostensibly refractory to epinephrine aminophyllin and a host of sedative preparations In one patient the respirations became quieter and more shallow following the first injection of morphine sulphate 10 mgm This improvement was short lived and a second injection of 10 mgm was administered approximately four hours later Shortly after this injection the respirations were described as comparatively quiet though tracheal rales were audible There was evidence of pink frothing sputum in the mouth Attempts at oral suction were of no avail and the patient died about two hours after the second dose of morphine was administered The second fatality followed three hours after the administration of morphine sulphate 15 mgm and atropine sulphate 0 4 mgm The respirations were described as quieter and there was evidence toward the end of tracheal rales and frothy sputum

The majority of fatalities which appear to follow the injudicious use of morphine or of morphine combined with atropine occur at night The attending house officer or physician has observed the progressive development of the status state and is at a loss for another therapeutic agent to bring relief He may furthermore be fatigued from the stress and strain of his other responsibilities as well Hence he may administer or order a hypodermic of morphine hoping to bring relief to the struggling gasping patient Relief may follow the first injection This may lull him into a false sense of security that permits him to order a repeat dose when he is called again some time later and informed that the patient is having a desperate struggle for his breath and is disturbing the ward or family The second hypodermic may be the fatal one

We find that dihydro morphine hydrochloride (Dilaudid) has a greater range of safety and less depression is observed with its use It is a more powerful analgesic has minimal hypnotic properties and is shorter acting than morphine It produces fewer side reactions and less euphoria Usually 1 5 mgm of Dilaudid may be given at twelve hour intervals for two or three days this procedure may be attended with striking amelioration of asthmatic distress The same dosage may be added to the rectal aminophyllin solution during the first few days of management of the patient in status asthmaticus

Meperidine hydrochloride (Demerol) also has a far wider range of safety than morphine and is a more efficacious drug in the treatment of the very sick asthmatic patient for it is extremely helpful in relieving an intractable or utterly useless cough It may be given in doses of 50 to 100 mgm intramuscularly or 100 to 150 mgm orally at eight or 12 hour intervals for three to five days The use of smaller doses at the outset may minimize any side reactions On rare occasions it may be placed directly in the intravaneous infusion Some bronchodilation and mild sedation may be observed atropine like effects may also occasionally be observed and a few patients will complain of nausea or of dizziness The majority of patients however enjoy a pleasant state of general relaxation following its use Tachyphylaxis is occasionally noted but full response usually returns after a rest period We have not personally seen any respiratory depression following its use Addiction to meperidine although less frequent than to morphine does occur and may be of a severe type

In the laboratory we have found meperidine to be a fair antihistaminic and a somwhat better anticholinergic drug (Fig 7) Following intramuscular administration of 100 mgm to five asthmatic subjects average peak pro-

tection of 65 per cent was reached within one hour and adequate protection (above 40 per cent) lasted for two and one half hours against the bronchospastic effects of acetyl beta methylcholine administered intravenously Protection against the effect of histamine was not as good al

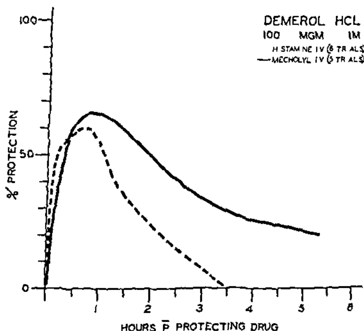


FIGURE 7 The Protective Value of Demerol Hydrochloride One Hundred mgm Given Intramuscularly against Histamine and Mecholyl Induced Dyspnea and Bronchospasm in Asthmatic Subjects

though significant protection lasted for one and one half hours *Scopolamine* (levo rotatory hyoscine) when administered subcutaneously has proven to be an excellent anticholinergic drug[33] (Chapter III) A combination which we have found effective clinically is meperidine hydrochloride 100 mgm and *scopolamine hydrobromide* 0 3 mgm—a modified form of "twilight sleep" However, I

would suggest that this combination be used with caution. I would avoid its use entirely in the dry asthmatic. In the wet asthmatic it may be attendant with striking success when first administered, but it should not be repeated more than twice in a 24 to 48 hour interval.

3. Avertin, Cyclopropane, Ether and Paraldehyde

The mechanism of bronchial relaxation with these agents is not entirely known. It seems that the complete mental rest which follows their use in some way inhibits reflex bronchial constriction. However, it is imperative that deep sedation or anesthesia not be employed for periods of more than one hour at a time in the treatment of severe bronchial asthma because of the possibility of the patient developing asphyxia or atelectasis. These complications may be prevented by employing inhalations of oxygen or of helium and oxygen mixtures.

Avertin (tribromethanol in amylene hydrate) administered rectally in doses of 60 to 75 mgm. per kilogram of body weight has been employed for the interruption of the asthmatic crises.[82] However, it is generally considered a dangerous anesthetic agent with a narrow range of safety.[30] Others have recommended the use of cyclopropane anesthesia (to the second stage) for the relief of paroxysms of bronchial asthma.[22, 154] There is evidence, however, that this agent may produce bronchoconstriction.[130] Cyclopropane as well as epinephrine may occasionally precipitate ventricular arrythmias, hence they should not be used together. For these reasons, avertin or cyclopropane are generally not recommended as anesthetic agents to be commonly employed for the management of severe bronchial asthma.

When sedation to the point of actual light anesthesia is required, ether is the anesthetic agent of choice and may

be administered high rectally in doses of 60 to 90 cc dissolved in an equal amount of sweet oil This dose may be repeated hourly for several doses if needed A larger single dose (90 to 150 cc) may be given at eight hour intervals for two or three days

Relief from *intractable asthma frequently follows the* mental relaxation and the increased expectoration induced by ether Barach has called our attention to the synergistic relaxing effects of helium and oxygen breathing and of rectal ether [9] Furthermore one may frequently observe restoration of epinephrine sensitivity in the epinephrine fast subject after he has been so treated Inhalation anesthesia with ether may be resorted to on rare occasions We have found intramuscular injection of ether in oil to be of no value

Paraldehyde should be used as an amnestic or hypnotic rather than as an anesthetic Paraldehyde should not be administered intravenously for deaths have been reported when this route has been employed [4] Post mortem examination of such fatalities and also of those reproduced in experimental animals showed dilatation of the right side of the heart with pulmonary hemorrhage and edema Clinically these fatal complications are preceded by signs of acute failure of the right side of the heart Intramuscular administration of paraldehyde should also be avoided because of the danger of accidental venipuncture and the possibility of ensuing cellulitis and abscess formation following the use of 10 to 20 cc of this drug We have found that the rectal route is the safest and the one best *tolerated A troublesome proctitis may* follow protracted use of ether or paraldehyde rectally Paraldehyde may be administered rectally at twelve hour intervals in doses of 20 to 30 cc combined with equal amounts of olive oil or prepared as a corn starch emulsion Similar doses prepared

in iced lemonade, may be given orally, however, many patients object to the taste and smell Rebreathing of paraldehyde vapor should be prevented in the sick or moribund patient confined in a tent or other closed chamber Frequently following the rectal use of paraldehyde or ether, coughing or a suddenly increased flow of mucoid secretions may be invoked, generally to the patient s benefit

I would like to complete the subject of sedation and anesthetic drugs by adding a few words of caution about the use of atomized or topical pontocaine and cocaine

1 Keep in mind the latent period of sensitization of one to four weeks following the use of these preparations Serious reactions or fatalities may follow second usage (particularly of pontocaine)

2 Skin testing, although of questionable value, should be done before using these drugs

3 Preliminary use of barbiturates and antihistaminics may minimize the extent of the reaction

4 Epinephrine and aminophyllin must be available for immediate administration

5 An aminophyllin infusion should be given prophylactically to all patients who are about to receive pontocaine or cocaine anesthesia for a second time within a one to four week period

CHAPTER V

SUPPORTIVE THERAPY

THE sick asthmatic patient presents a serious picture of marked physiologic imbalance Severe hypoxia cyanosis *dehydration peripheral vascular shock and drug intoxi*cation from intensive therapy may all be present Disturbance in water and electrolyte balance usually exists which makes absorption of liquids uncertain whether given orally or subcutaneously Because of dyspnea and rapid gasping respirations the patient finds it difficult to take adequate quantities of water or other fluids orally Anorexia and the proclivity for abdominal distension contribute further to this difficulty What little fluid and electrolytes he is *able to ingest or store up may be depleted by vomiting* excessive sweating and through respiration Combined water and salt depletion usually ensues if adequate therapy is not employed

I Replacement Therapy (*water glucose saline infusions*)

The fluid intake and output should be measured and recorded in all of these patients An adequate urine volume of not less than 1 500 cc per twenty four hours *should be maintained The physician should treat the* patient rather than his blood chemistry He should however understand the manifestations of water and salt deficit namely dehydration weakness fever psychotic manifestations oliguria with attendant high specific gravity of urine rise in blood urea nitrogen hematocrit and plasma proteins fluctuations of blood chloride and sodium concentrations and eventually circulatory failure

and death The dehydration tends to increase the viscosity of the muco purulent exudate This may lead to actual bronchiolar impaction and segmental atelectasis The ineffectual cough disturbs the patient and contributes greatly to his mental and physical fatigue

The primary requisite is replacement of the lost fluid and electrolytes The minerals in the fluids administered will supply the lost electrolytes the fluid itself will hydrate the patient improve urinary excretion and help to regulate body temperature This may be done most efficiently with intravenous therapy No fixed rules should be established for the composition of this so called intravenous cocktail The replacement fluid both in volume and composition depends upon the age of the patient the degree of dehydration and of bronchospasm the cardiac and renal status and individual tolerance to drugs and to venipunctures It is generally my custom to begin by using 5 per cent glucose in isotonic sodium chloride solution for the first liter and 5 per cent glucose in distilled water for the second and third liters Three liters may be given in 24 hours by employing a flow of approximately 30 drops per minute In the young patient in whom the possibility of chronic cor pulmonale and underlying heart disease does not present itself one can safely replace the second liter of distilled water with isotonic sodium chloride solution When there is evidence of severe depletion with acidosis Hartman s solution (1 6 molar racemic sodium lactate) may be employed until the CO (volumes per cent) returns to normal

2 The Role of Digitalis and Mercurial Diuretics

In the patient with a complicating chronic cor pulmonale the judicious use of a salt free diet the elimination of sodium chloride from the intravenous cocktail

and the use of intramuscular injections of one of the mercurial diuretics have been of life saving value I have found Mercuhydrin (N(3 methyl 2 oxy mercuripropyl) N succinyl urea) to be an effective nontoxic diuretic Acidification of the urine with ammonium chloride may double its diuretic effect

On the whole I have not been able to convince myself of the value of digitalis in most of these patients with emphysema and cor pulmonale Although an occasional patient appears to be helped some are even further incapacitated and disastrous results may occasionally follow attempts at rapid digitalization The value of digitalis in these patients can be largely predicted from experimental studies of the cardiac output and venous pressure McMichael and Sharpey Shafer [7, 9] called attention to the *fact that patients with emphysema and cor pulmonale with* gross venous congestion and very low arterial oxygen saturation may have a high cardiac output (high output heart failure) They suggested in their studies that digitalis in these subjects may lower the venous pressure and with it the cardiac output Reductions of the latter would disturb the output necessary to compensate for the marked resistance to pulmonary blood flow in these patients However in the later stages of cor pulmonale left ventricular failure and pulmonary edema may occur and digitalis preparations would be of value More definitive studies of cardiac and pulmonary function similar to those being made by Cournand [56, 58] McMichael[117, 119] and their associates utilizing cardiac catheterization may ultimately shed more light on the exact value of digitalis in the treatment of pulmonary emphysema and cor pulmonale

3 Aminophyllin Infusions

Aminophyllin (theophyllin ethylene-diamine) in varying dosage may be added to the intravenous infusion

Theophyllin[84] has been demonstrated to cause relaxation of bronchial spasm and to lower intravenous and intrathecal pressures It is also a potent diuretic and generally stimulates the central nervous system We[40] have been able to demonstrate that aminophyllin exerts an appreciable antihistaminic effect but a very moderate anticholinergic effect in protecting against histamine and mecholyl induced dyspnea and bronchospasm in asthmatic subjects Goodall and Unger[88] have been able to relieve many severe attacks of bronchial asthma with continuous intravenous aminophyllin in glucose or saline solutions

Patients vary in their tolerance to aminophyllin some become alerted others become drowsy many become nauseated and may even vomit and still others complain of palpitations and sweating Syncope and peripheral vascular collapse may be observed if the rate of injection is too rapid Some of these reactions may be avoided by slowing the rate of flow One may begin by adding 0 5 gm of aminophyllin to the first liter of solution The dose may then be decreased or increased to 1 gm per liter of solution depending upon the patient s tolerance How long should one continue to use intravenous aminophyllin? Infusions may be run continuously for as long as 10 days The duration should depend entirely upon the patient s response and tolerance to aminophyllin If improvement results after one or two days of continuous therapy infusions may then be given intermittently e g from 9 A M to 9 P M daily reducing the total intake to 1 500 cc This schedule does not interfere with the patient s freedom of motion at night Supplementary aminophyllin if necessary through the night may be given in the form of a 20 cc intravenous solution containing 0 25 or 0 50 gm aminophyllin This should be administered slowly at a rate not exceeding 2 0 cc per minute The patient may sit in a comfortable arm chair and a moderate degree of amb

tion during the infusions may be allowed The dorsum of the hand is best suited for intravenous therapy in asthmatic subjects as this site permits a greater range of arm motion and less danger of obstruction or dislodging the needle during coughing paroxysms A different vein or segment should be selected from day to day The use of distal venous segments minimizes the danger of thrombosis of all available veins—an appreciable factor when veins in the antecubital fossa are used

The moderately ill asthmatic suffering from an acute attack which has not responded to epinephrine previously administered in one form or another usually benefits greatly by one or more intravenous injections of 0 5 gm aminophyllin in 20 cc of distilled water These may be repeated at intervals of eight or 12 hours If they become necessary one or more times daily for as long as one week the continuous infusion technique should be started

The continuous or interrupted infusions may be omitted when there is evidence of complete freedom from severe paroxysms of coughing or bronchospasm In their place aminophyllin should then be administered rectally[31] in dosage of 0 3 to 0 6 gm in 15 cc of tap water every eight or 12 hours This therapy in gradually diminishing dosage should be continued for at least one month after complete recovery I have kept patients on maintenance programs with rectal aminophyllin solution for as long as two years with no demonstrative ill effects and with freedom from recurrent attacks In time the rectal aminophyllin solution may be replaced by an oral tablet containing aminophyllin 0 2 gm ephedrine sulfate 0 025 gm and sodium pentobarbital 0 03 gm

Intramuscular aminophyllin (2 0 cc ampoule containing 0 5 gm) has proven of negligible value clinically and

furthermore patients complain of pain during its administration and of residual soreness and lumps. I have not found aerosols of aminophyllin employing the same ampoule with the disagreeable bitter taste disguised by adding several drops of peppermint water of sufficient value to warrant the necessary expense and technical detail involved.

4. Ascorbic Acid, Cytochrome C and Nicotinic Acid

Other therapeutic agents may be added to the intravenous cocktail. Ascorbic acid or Cytochrome C[134,135] have been given intravenously as respiratory catalysts by various investigators in the hope that these agents will increase the oxygen uptake from the blood plasma into the red cells themselves. No striking results have been seen from their use although as much as 5,000 mgm. of ascorbic acid per liter of isotonic sodium chloride solution and 100 mgm. of Cytochrome C have been given intravenously every eight hours for one week to several patients in status asthmaticus. Occasionally one may witness a very prompt response with ascorbic acid but it is quite difficult to attribute this to the drug. The same observations hold true for nicotinic acid intravenously. In a small but representative series of 18 patients in status asthmaticus I could not convince myself that any striking improvement resulted from its use. One may observe an extensive flush and perhaps some bronchial dilatation but no lasting effects. Furthermore the side reactions of flushing, warmth and throbbing headaches are not well accepted by most patients although they were forewarned of same. The intravenous use of Vitamin B Complex preparations should be avoided because of the possibility of sensitization to thiamine hydrochloride.

5 Alcohol Dextrose Infusions

On occasion an alcohol dextrose solution may be given intravenously in place of isotonic sodium chloride dextrose infusion Brown[43] and Brown and Gillespie[44] have reported excellent results with infusions of 5 per cent ethyl alcohol in glucose or saline with or without epinephrine in the solution I have generally employed one liter of 5 per cent ethyl alcohol in 5 per cent glucose solutions free of vitamin supplements When necessary aminophyllin is added to this infusion Flows of 80 to 120 drops per minute are generally necessary for relaxation Excitement may follow too rapid rates and relaxation may fail to occur with slow rates this is due to excessive or inadequate cerebral blood levels respectively Occasionally striking relaxation may be observed when the mixture is given for the first or second time As a rule however, these effects do not persist with repeated use Moreover the peripheral vasodilatory effects which may occur could be deleterious in the presence of peripheral vascular collapse and thus further limit the usefulness of this mixture

6 Blood Plasma

I have observed in this series of 513 patients with bronchial asthma three instances of severe peripheral vascular collapse characterized by ashen colored cold and clammy skin rapid and barely perceptible pulse and falling blood pressure These patients were given blood plasma with very good effect Two patients required two units each and the third patient received eight units in 24 hours before recovering from profound shock The sternal route had to be employed with the last patient because of inability to utilize the collapsed veins when death appeared imminent I would caution against exceeding 3 000 cc for the total 24 hour dose because of the danger of acute

left ventricular failure Supplemental oxygen intravenous neosynephrin ascorbic acid and adrenal cortical hormone were also employed in these patients Recovery in all cases was complete

7 Antihistaminic Preparations

We[134] have been able to demonstrate with many of the new antihistaminic (histaminolytic) preparations excellent protection against experimental histamine induced dysp nea and bronchospasm in asthmatic subjects These are ideal blocking agents in that they prevent the histamine from reaching the receptor mechanism in the cell where it exerts its characteristic effects However these prepara tions do not prevent the intracellular release of histamine Furthermore because of failure of absorption or due to inactivation in the gastro intestinal tract orally ad ministered antihistaminic agents may fail to block the action of freely circulating histamine For these reasons orally administered antihistaminic agents may afford only limited relief in the routine management of the acutely ill asthmatic patient On the other hand when ad ministered intravenously these agents can effectively block the action of freely circulating histamine

The antihistaminic agents may be of particular value in the following instances

I Orally—for the relief of nasal obstruction (allergy is the dominant factor in the maintenance of chronic para nasal sinus disease in the asthmatic patient) Para nasal sinus disease is responsible for the recurrence of cough and wheez ing in many patients with bronchial asthma Patients with para nasal sinus disease are more likely to have irreparable sino-bronchitic disease and serious bronchial asthma In the acutely ill asthmatic nasal obstruction and post nasal drip contribute further to the dyspnea and cough already

present The antihistaminic preparations in doses of 25 to 100 mgm orally at six hour intervals help considerably in relieving the nasal obstruction and secondary cough We have on occasion employed aerosols of 2 per cent tripelennamine hydrochloride (Pyribenzamine hydrochloride) nasally in these patients with good effect If infection is present aerosols of an antihistaminic agent and penicillin employing the technique of intermittent negative pressure[23] and replacement with the aerosol should be tried

II Intravenously—for the relief of bronchospasm in the ambulatory patient having an acute asthmatic paroxysm The unfavorable reports concerning the clinical effectiveness of the antihistaminics in hay fever and bronchial asthma may to a great extent be influenced by the variability of absorption incident to the routine use of the oral route We have observed in the laboratory that a number of patients demonstrated no significant antihistaminic effect in the protection afforded against histamine induced bronchospasm and dyspnea when the antihistaminic drugs were taken orally whereas significant protection occurred when the intravenous rectal or aerosol routes were employed with the same agents On the basis of these observations we administered diphenhydramine (Benadryl) or tripelennamine HCl (Pyribenzamine) intravenously (30 trials in six patients) to observe particularly any bronchospasmolytic properties of these drugs Prompt relief from the asthmatic paroxysm with increases of more than one liter in the patients vital capacity was uniformly observed These patients were asthmatic subjects employed in our protection studies who demonstrated spontaneous asthma while in the laboratory awaiting study or at home

III Intravenously—to restore the delicate histamine sympathin balance in the so called epinephrine refractory state We[64a, 65a] employed intravenous diphenhydramine hydrochloride (Benadryl chloride) or tripelennamine hydrochloride (Pyribenzamine hydrochloride) in a series

of 10 patients acutely ill in status asthmaticus The injections were given slowly at a rate of about 1 cc per minute either directly or via the constant intravenous infusions (aminophyllin glucose-saline or distilled water) Doses of 30 to 50 mgm (10 mgm per cc of solution) at four to eight hour intervals were administered and continued for one to four days To avoid pharmacologic incompatability the antihistaminics were injected directly into the rubber tubing close to the intravenous needle With improvement the dosage was gradually reduced to 20 mgm every eight hours and then finally discontinued A total of 62 injections were given to these patients The most striking effect observed was what appeared to be restoration of epinephrine sensitivity Following these injections epinephrine administered subcutaneously or by the aerosol route appeared to bring relief from an acute paroxysm of bronchospasm whereas previously following an aminophyllin glucose saline or distilled water infusion only the side effects of epinephrine were observed following its use The mechanism involved may have been the potentiation of adrenergically controlled functions by the antihistaminic agent This will be discussed in Chapter VI

II Intravenously—for sedative effects in status asthmaticus When intravenous diphenhydramine was employed in this group of patients its sedative properties were pronounced Generally a more relaxed feeling and short periods of sleep followed each injection The additive effects of sedation and restoration of epinephrine sensitivity were more important factors in the recovery of these patients

We[34 169] have tested a wide variety of antihistaminic drugs and combinations for their protective value against histamine and acetyl beta methyl choline chloride induced dyspnea and bronchospasm One example is presented here Figure 8 depicts the degree of protection that is afforded against intravenous histamine and acetyl beta

methylcholine chloride and histamine aerosol by a combination of diphenhydramine 50 mgm and aminophyllin 200 mgm (Hydryllin Searle) in two tablets taken orally. The histamine curve represents five trials in five subjects; the acetyl beta methylcholine chloride curve, six trials in

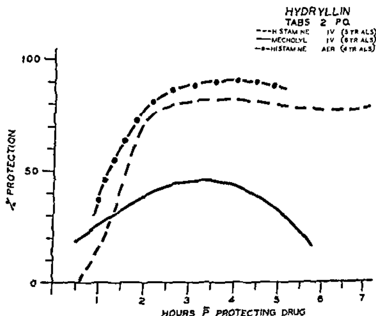


FIGURE 8 The Protective Value of Hydryllin Two Tablets Given *Orally Against Histamine- and Mecholyl Induced Dyspnea and Bronchospasm in Asthmatic Subjects*

six subjects. It is our clinical impression that protection levels of 40 per cent or higher represent a real difference in the reaction to the bronchospastic agent; this is applicable to all patients thus far tested. Accordingly, this level may be a significant one in comparing the effectiveness of various protecting drugs. Significant protection against

histamine is not achieved until one and one-half hours after the oral administration of *two tablets* of Hydryllin It rapidly *reaches* levels of *complete* protection and *remains complete* for seven hours which is the longest *period* we have studied this *phenomenon*

The *protection* against mecholyl chloride is less ideal for it does not reach a 40 per cent level until after two hours it remains at a significant level for two hours more and then falls off rapidly in the fifth hour after administration of the protecting drug No drowsiness is noted from *this* oral medication Side *effects* consistent with the *injection* of histamine are *markedly decreased* during the interval of full *protection*

The recent observations of Hambourger and his associates[98] in their study of the protective action of combinations of diphenhydramine and aminophyllin in fatal bronchospasm in guinea pigs due to mecholyl aerosol is timely and pertinent to our studies just described They found diphenhydramine and aminophyllin *alone or* in combination effective in preventing the fatal bronchospasm induced in guinea pigs by *aerosols* of mecholyl When *used in combination* the *protective* and *intraperitoneal lethal* actions were truly *additive in nature For* protection they found 1 gm of *diphenhydramine equivalent* to 3 22 gm of aminophyllin In the case of intraperitoneal toxicity 1 gm of diphenhydramine was equivalent to 2 17 gm of aminophyllin *It* must be *recalled however* that the mode *of action* of these two drugs is *different*

The clinical *management of the chronic* asthmatic may be tremendously *facilitated by the use of* aminophyllin This *drug* relaxes the bronchial musculature and stimulates the central nervous system thus theoretically reducing the incidence of depression in these centers that is frequently seen with antihistaminic agents In addition

the diphenhydramine present in Hydryllin may act to prevent or alleviate the allergic wheal or 'bronchial hive' of the asthmatic In addition to the powerful antihistaminic and weak antichloinergic properties of diphenhydramine it is also known to exert considerable antispasmodic action and to potentiate the effect of epinephrine to some degree Correlation of the laboratory protection afforded by Hydryllin with the practical management of clinical asthma is a slow process Many patients who have been taking Hydryllin regularly have found it of considerable value in reducing the frequency and severity of attacks

CHAPTER VI

EPINEPHRINE

PRODUCTION of symptomatic relief from a paroxysm of bronchial asthma is by no means as uncomplicated as is generally represented. Chief reliance is in the administration of epinephrine or other sympathomimetic amines.

1 The Use of Epinephrine

Epinephrine has proven to be an excellent protecting agent against dyspnea and bronchospasm induced experimentally with histamine and mecholyl chloride in our laboratory.[41] This drug has been employed in various modifications, concentrations and routes. No true idiosyncrasy (allergy) to epinephrine has been reported. However, toxic reactions, intolerance, and fastness may occur. These effects are more commonly observed with repeated use and with overdosage.[7, 156] Deaths have been reported following intravenous administration or accidental intravenous injection; these fatalities may have been due to epinephrine deposition in the heart muscle with ensuing ventricular tachycardia and fibrillation.[12] A warning should be made about the possibility of accidents from the injection of 1:100 epinephrine and other concentrated sympathomimetic amines intended purely for aerosol use. Moller of Copenhagen discussed the subject of acute epinephrine poisoning and reported the successful recovery of a 12 year old girl who had accidentally received twice the fatal adult dose (20 mgm. of epinephrine: 0.2 cc. of a 10 per cent solution). He attributed this recovery to the persistent use of nitrites as peripheral vasodilators and epinephrine antagonists. He recommends giving in

halations of amyl nitrite vapor (3 minims) as quickly as possible followed by a larger dose (2 0 to 4 0 mgm) of oral nitroglycerin and then intravenous erythrol tetranitrate in divided doses of 5 0 mgm to a total of 20 0 mgm to control the elevated blood pressure and promote recovery according to individual requirements A tourniquet should be placed proximal to the site of the original injection and intermittently released However if acute epinephrine toxicity has resulted in peripheral vascular collapse (due possibly to its sympathin I action) the use of these powerful vasodilators may potentiate the shock

Epinephrine may be injected subcutaneously in doses of 0 2 to 0 3 cc of 1 1 000 concentration Relief is generally observed in five to 15 minutes following its administration It may be given intravenously in doses of 0 5 to 1 cc of 1 1 000 concentration in a liter of saline or preferably it may be nebulized in 1 100 concentration [80] For slow release it may be given intramuscularly in an oil or gelatin base in doses of 0 5 to 1 0 cc of 1 500 concentration after shaking thoroughly I have not observed any striking value from these combinations of epinephrine (1 500) Their value is limited by the uncertainty of uniform absorption and action due to the sudden release of epinephrine the side reactions the residual soreness and possible oil tumors

In general epinephrine parenterally is limited in its value to the relief of the acute attack The minimum dosage which will accomplish the desired effect is the best for it will also minimize the disagreeable side reactions Unfortunately few limit the dosage to the proper and effective subcutaneous injection of 0 2 0 3 cc of 1 1 000 dilution Generally larger doses at unnecessarily frequent intervals are employed The use of the hypodermic needle for self medication which should be avoided is too often

encouraged Habitual users of self administered hypodermics of epinephrine become dependent upon this crutch which further contributes to the despair of the disease The epinephrine fast state is encountered most commonly in these patients They frequently present altered personalities (a prematurely aged appearance) signs of vasomotor instability irritability palpitations tachycardia and transient hypertension As most patients in status asthmaticus are epinephrine fast the use of all epinephrine preparations should be avoided for at least several days until epinephrine sensitivity is restored I have made a rule of never adding epinephrine to the intravenous cocktail for these patients

2 The Epinephrine Refractory State

The development of the epinephrine-fast state in the asthmatic subject is distressing to the patient and is poorly understood by his physician The delicate histamine sympathin balance or seesaw is upset Repeated injections of epinephrine no longer produce bronchial relaxation but rather manifestations of toxicity—namely palpitations tachycardia headache flushing etc Staub[181] and Farrerons Co[78] have demonstrated that epinephrine provokes the production or release of histamine in the experimental animal (probably as a homeostatic effort) Yonkman[204] and Yonkman and Mohr[2 5] thought that these studies probably explained in part the mechanism involved in the potentiation of adrenergically controlled functions by antihistaminic agents and furthermore that this histamine release could paradoxically contribute to further bronchoconstriction pulmonary edema and dyspnea This sequence for some reason may be more pronounced in the allergic than in the normal subject They suggested that antihistaminic preparations given intravenously could be

of value in serving as histamine antagonists or epinephrine sparers in the epinephrine resistive patient thus balancing the delicate histamine sympathin seesaw These studies by Staub Farrerons Co and Yonkman and Mohr are of particular interest in view of our recent observations in 10 acutely ill patients in status asthmaticus[164a, 203a] described above (Chapter V) Restoration of epinephrine sensitivity followed the intravenous injection of 30 to 50 mgm of an antihistaminic in these subjects Injections were repeated at four to eight hour intervals for one to four days Parenteral and aerosol epinephrine appear much more efficacious following these injections

3 Ephedrine Preparations

The use of ephedrine preparations for the relief and prevention of asthmatic attacks has many limitations They are of no value in the acutely ill patient Side reactions notably palpitation headache jitteriness and insomnia are quite common In male patients urinary difficulties particularly dysuria and diminution of the urinary stream may appear due to spasm of the prostatic sphincter However preparations employing ephedrine sulfate or similarly acting drugs combined with antihistaminics or theophylline ethylenediamine and sedative preparations are beneficial as supplementary therapy for the ambulatory mild chronic asthmatic patient Continuous use should be avoided and omission for two days of each week is recommended Several of the newer ephedrine like synthetic drugs may produce fewer side reactions One of these preparations Orthoxine (Upjohn) has been well tolerated in 200 mgm doses at four hour intervals and has appeared to help some patients[41, 115] Moreover we have demonstrated with its use approximately the same degree of pro-

tection as ephedrine sulphate against experimentally induced dyspnea and bronchospasm[41] (Fig 9)

The protective value of ephedrine sulfate (25 mgs p o) against the bronchospastic effects of intravenous histamine and intravenous mecholyl was studied in four patients

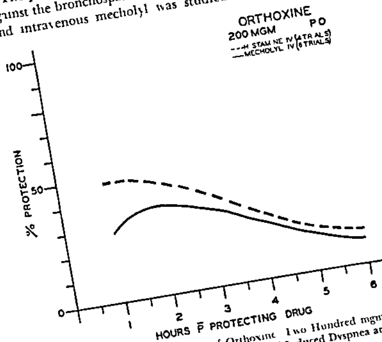


FIGURE 9 The Protective Value of Orthoxine Two Hundred mgm Given Orally Against Histamine and Mecholyl Induced Dyspnea and Bronchospasm in Asthmatic Subjects

(Fig 10) It proved to be a poor protecting agent against mecholyl chloride induced dyspnea and bronchospasm and a relatively fair protecting agent against histamine induced dyspnea and bronchospasm Adequate protection (10 per cent) was observed at the end of one and one half hours A slightly higher degree of protection (40 to 55 per

cent) persisted for approximately the same length of time and then fell off sharply

Having studied the protective capacity of antihistaminic preparations alone and combined with aminophyllin and ephedrine preparations alone, *we decided to study the protective capacity* of an antihistaminic preparation combined with ephedrine sulphate The combined oral administra

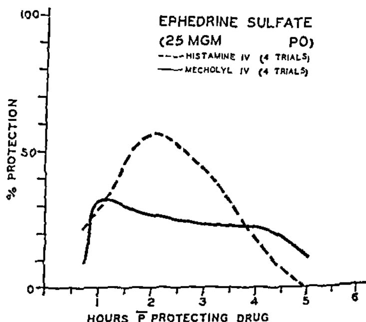


FIGURE 10[41] The Protective Value of Ephedrine Sulfate 25 mgm Given Orally Against Histamine and Mecholyl Induced Dyspnea and Bronchospasm in Asthmatic Subjects

tion of a *sympathomimetic agent ephedrine sulphate* (25 mgm) and an antihistaminic diphenhydramine (Benadryl 50 mgm) demonstrated an additive protective action against the effects of mecholyl and histamine *which exceeded* the protective value offered by either drug ad

ministered alone This synergistic effect as observed in the laboratory would suggest that improved clinical relief may follow their combined use

I have found a tablet containing aminophyllin 0 2 gm ephedrine sulfate 0 025 gm and sodium pentobarbital 0 03 gm (administered upon arising and again at 3 P M if indicated) very helpful as a supplementary measure in the recovery state The pentobarbital serves as an efficient sedative capable of offsetting the stimulatory effects of aminophyllin and ephedrine In one patient we were able to demonstrate adequate protection (40 to 50 per cent) against the bronchospastic effects of intravenous histamine this degree of protection appeared one and one half hours after the administration of one tablet p o and lasted for two and one half hours In the same subject adequate protection against the effects of intravenous mecholyl appeared two and one half hours after administration and lasted for a similar length of time A tablet containing aminophyllin 0 3 gm ephedrine sulfate 0 04 gm sodium pentobarbital 0 1 gm and phenobarbital 0 06 gm may be administered at bedtime for prompt and protracted hypnotic action

CHAPTER VII

THE THERAPEUTIC USE OF GASES

1 Oxygen

FOR the acutely ill or status asthmaticus patient demonstrating evidence of hypoxia and cyanosis oxygen in concentrations of 95 per cent or more administered with the O E M meter mask may be employed (Figs 11 and 12) This mask is a distinct credit to the ingenuity of its inventors and is of tremendous practical value[27] An air injector (concentration meter) provides accurately controlled air oxygen mixtures in whatever proportion is indicated Rebreathing and carbon dioxide accumulations are

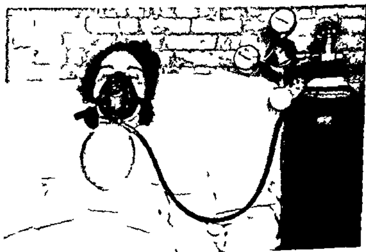


FIGURE 11 Meter Mask (Oro nasal type) for the Administration of Controlled Concentrations of Oxygen or Helium Oxygen Mixtures *Positive Pressure in Expiration May Be Employed if Indicated*

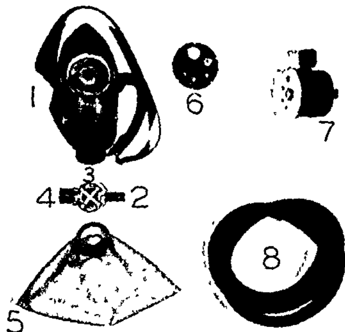


FIGURE 12 Parts of Meter Mask

1 Comfortable Oro-nasal Face Piece with One way Expiratory Flutter Valve
2 Oxygen Inlet Tube
3 Unidirectional Mica Valve which Prevents Rebreathing May be Seated or Removed if Rebreathing is Desired as with Helium Oxygen Therapy
4 Accessory Mica Inlet Valve Permits Room Air to Enter when Inadequate Oxygen Flows are Entering Collecting Bag
5 Rubber Collecting—One or Two Liter Size
6 Disc Metered for Positive Pressure (1 to 4 *cm* water) in Expiration Only Expiratory one way Flutter Valve Seated Within
7 Oxygen Concentration Meter (40% to 95%) Also serves as Humidifier
8 Special Gage Rubber Connecting Tubing

totally eliminated by means of an inspiratory valve at the entrance to the face piece from the collecting bag and an expiratory valve in the face piece itself (which incidentally is unusually comfortable) Mechanical resistance to respiration is greatly reduced by this arrangement of valves A large soft latex collecting bag of 1 or 2 liter capacity makes it possible for the patient to breathe deeply with comfort In addition the face mask has an attached expiratory outlet that has been metered for positive pressure in expiration up to 4 cm of water pressure A higher positive pressure may develop in the face-piece during dyspnea when the 4 cm orifice is used The apparatus can be used to deliver 40 to 95 per cent oxygen or helium and oxygen mixtures with or without positive pressure If carbon dioxide therapy is desired the inspiratory valve may be removed to allow rebreathing I have used this apparatus in various types of cardio respiratory disease and find it practical and economical [160 161 162]

Under normal conditions the inhalation of 100 per cent concentrations of oxygen has no deleterious effect on tissue function provided it is not maintained continuously for longer than twelve hours Inhalations of 50 to 100 per cent concentrations of oxygen increase the partial pressure of oxygen in the lung thus making it possible for the blood to absorb and transport a quantity of gas greater than the normal The hemoglobin saturation can be raised from 96 to practically 100 per cent and the oxygen in simple solution in the plasma from 0 3 per 100 cc of blood to a maximum of 2 2 cc This represents a possible increase of as much as 15 per cent in the oxygen carrying capacity of the blood throughout the circulatory system This in turn produces a corresponding increase in the partial pressure available for the diffusion of oxygen from the blood into the tissues In this connection Campbell and

Poulton[48] have demonstrated that the oxygen pressure in tissue is increased proportionately more than is the oxygen content of the blood This increase in oxygen content in the blood and oxygen pressure in the tissues is observed best in hypoxic patients in whom the oxygen carrying capacity of hemoglobin may increase from low levels of 50 to 75 per cent to 85 to 90 per cent when high concentrations of oxygen are inhaled

Evans[46] has for many years repeatedly described beneficial clinical results from so called 100 per cent oxygen in severe hypoxia Concentrations of 70 to 100 per cent should be used when lower concentrations are insufficient In extensive clinical observations on approximately 800 patients Boothby and his associates[38, 40] employed high concentrations of oxygen for periods as long as forty eight hours without any evidence of pulmonary irritation However they did warn against continued administration for a period longer than 48 hours Further clinical investigation showed that high concentrations can be used with relative safety for periods of two to five days when a mask apparatus is employed since mask therapy is really not continuous inasmuch as the mask is frequently removed for general nursing care feeding etc

In closed respiratory chambers such as the helium and oxygen hood apparatus (Fig 13) it is inadvisable to use continuous oxygen concentrations of above 70 per cent for more than 18 hours [8, 20] If oxygen therapy must be maintained for longer periods a special air injector attached to the oxygen regulator provides accurately controlled air oxygen mixtures The sleeve vents of the hood should be opened to allow the entrance of room air for one half hour every three or four hours when this injector is not employed Oxygen toxicity from the inhalation of high concentrations can occur in hypoxic patients However when

ever indicated high concentrations can be safely given for periods at least as long as one week with the mask apparatus and intermittently for the same length of time with the hood apparatus

Many acutely ill patients in status asthmaticus cannot tolerate mask therapy They complain of a sense of suffoca

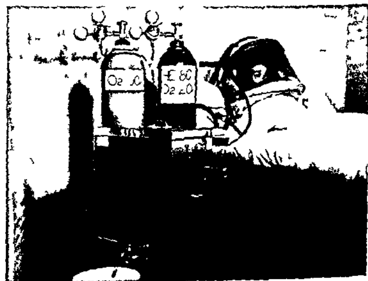


FIGURE 13 Hood Apparatus—(Oxygen or Helium Oxygen Positive Pressure Breathing)

tion or claustrophobia and furthermore many object to the smell and sensation of rubber near them If hypoxia is not severe a simple large cellophane type of face tent or conjoined bent catheters fitted to the nares may be used to administer up to 40 per cent concentrations of oxygen in flows of 5 to 8 liters per minute Adequate humidification is necessary to prevent the drying and irritant effects of oxygen so administered If one uses the catheter method it is well to employ a simple water bottle humidifier Many

prefer a diffusion head inlet and a water trap outlet type of humidifier Adequate water vapor concentrations can be obtained with the use of the concentration meter when employing the O F M mask If higher humidity is desired the injector may be removed and a water bottle type of *humidifier substituted*

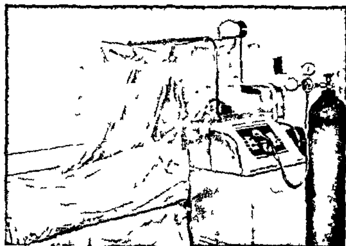


FIGURE 11 Mechanaire Type Iceless Oxygen Tent

I prefer the use of an oxygen tent with a transparent canopy enclosing the entire bed (Fig 11) The freedom of motion and the uninhibited feeling of being able to see all that goes on is well appreciated by the sick patient This type of tent which employs electrical refrigeration *affords more adequate air-conditioning humidity control* and ventilation without direct drafts on the patient s face It is simple to operate and eliminates the need for ice and skilled personnel Oxygen concentrations of 60 to 70 per cent may be maintained particularly if the motor is shut

off while the vents are opened to prevent circulation in the tent and consequent loss of oxygen It is my general custom to place the patient in the tent immediately upon arrival at the hospital Residence should be continued until recurrent attacks of *severe bronchospasm have subsided* The return to room residence should be gradual if severe emphysema is present If obstructive phenomena persist the patient may be removed from the tent for intermittent positive pressure helium oxygen therapy three or four times daily Whenever indicated a nebulizer apparatus for administering therapeutic aerosols may be introduced through a vent opening in the tent and the nebulizer placed in the patient s mouth

2 Helium Oxygen Mixtures

As Barach originally observed the inhalation of helium and oxygen mixtures relieves many patients who fail to respond to other recognized therapeutic measures [12 3] These observations have been confirmed by Boothby and his associates Rowe [38 40 116 15] Abramson [1] Schwartz [158] Goldsmith [87] Eyermann [77] and Metz [2] We have also been able to confirm these observations in a series of patients with severe bronchial asthma gas poisoning pulmonary edema atypical pneumonia and postoperative obstructive respiratory disease [160 161 163]

Helium is an inert non combustible gas of very low molecular weight (4) and is about one-seventh as heavy as air It has a low coefficient of solubility and is 2 7 times more diffusible than nitrogen hence only a small amount is dissolved or lost in the body A mixture of 80 per cent helium and 20 per cent oxygen is one third as heavy as air This lightness suggested to Barach that it could be *moved more easily to and from the lungs* in obstructive dyspnea During quiet breathing the influence of such a

decrease in weight is practically negligible However with respiration obstructed an increased negative pressure within the chest becomes necessary for the inward movement of air past the obstruction The pressure required for the movement of an 80 per cent helium 20 per cent oxygen mixture through a given orifice would be about half that required for air Barach demonstrated this phenomenon in normal individuals breathing through a resistance and in patients with heart disease breathing through minimal resistances Thus the principle of substituting helium for nitrogen in respirable mixtures was placed on a firm physiological basis for the treatment of respiratory obstruction from the larynx to the bronchioles With helium oxygen mixtures it should be possible to compensate for approximately 50 per cent constriction in the lumen of the tubal respiratory tract It is noteworthy that the more localized the obstruction the better the effect This decrease in respiratory effect may be accompanied by a progressive relaxation of the constricted bronchi and may be of life saving value

The type of gas mixture used will depend upon the factors responsible for the dyspnea (hypoxia or mechanical obstruction) If mechanical obstruction exists mixtures of 80 per cent helium and 20 per cent oxygen are more beneficial than oxygen alone The percentages of the helium and oxygen mixtures can be controlled at will by using separate tanks of oxygen and 80 per cent helium with 20 per cent oxygen connected by a Y tube to the apparatus used Tanks of helium alone should never be employed because of the danger of asphyxia should the oxygen supply become interrupted and the patient thus receive only 100 per cent helium The greater the concentration of helium (66 to 80 per cent) the more effective is the mixture in overcoming respiratory fatigue and dyspnea provided that hypoxia is avoided

The voice changes caused by effective helium and oxygen administration may be amusing or frightening to the uninitiated. The effect on man can best be described by the term "effeminate." A deep baritone voice develops a lyric tenor quality, and a man with a tenor voice can only squeak.[51] This has been explained as due to the fact that the muscles of the larynx are unconsciously set to cause a certain sound in air and that when breathing a medium so much lighter, the sound produced is much changed from normal.[206] Dublin, Baldes and Williams[73] made oscillographic studies on these voice changes. They determined that the alterations consist of a variation in overtones. The frequency of the fundamental vibrations remains the same. The low density of the helium and oxygen mixture impedes the vibration of the vocal cords less than does air. This may result in a change in the original overtones. Also, because of the lower density, the velocity of sound with helium and oxygen mixtures is increased. This probably causes the vocal resonators to amplify different overtones. Which of these differences is more important was not determined. Such changes are fortunately not permanent.

The helium and oxygen hood rebreathing apparatus is the most effective one for administering oxygen or helium and oxygen mixtures with or without positive pressures.[20, 75] The percentage concentrations of the mixtures can be exactly controlled. Positive pressures up to 6 cm of water can be applied to the inner surface of the lung during both inspiration and expiration. The apparatus (Fig. 13) consists of a gas tight motor blower, two canisters for the carbon dioxide absorber, a rheostat to determine the volume of air flow and its temperature, tubal connections, an ice containing cabinet and a plastocele head hood with a closure effected by a soft rubber neck collar

When this rebreathing circuit is in use, only the oxygen is utilized cooling de-humidification and removal of the carbon dioxide are efficiently performed I have found this apparatus very valuable in the treatment of severe bronchial asthma various types of pulmonary edema and obstructive dyspnea [161 162 163 165]

3 Positive Pressure Therapy

Positive pressure therapy generally employing a mixture of oxygen and helium has not received the wide spread use it deserves This therapy is indicated in the treatment of various types of pulmonary edema bronchial asthma and obstructive respiratory disease Barach and his associates[14 16 25 28 29 105] established the clinical application and usefulness of positive pressure and the physiologic factors involved in the treatment of obstructive dyspnea and acute pulmonary edema They devised the two types of apparatus previously described one (the hood) providing positive pressure during both phases of the respiratory cycle [25] and the other (the mask) during expiration alone [2] Signs of pulmonary edema rapidly disappear and remain absent as long as the pressure is applied or until the original cause is removed The application of a gentle internal distending force serves to keep the bronchioles patent and opposes the hydrostatic pressure within the capillaries Barach compared this process to that of putting a finger on the capillary wall itself He demonstrated by its use a reduction of the pathologically elevated negative intrapleural pressure present during the inspiratory cycle in patients who have developed pulmonary edema during obstruction of the air passages and frequently a lowering of the total pulmonary ventilation He observed other modifications in circulatory function particularly a diminished flow of blood into the right side

of the heart in patients with pulmonary edema These modifications which tend to prevent overfilling of the heart are similar to those seen when a tourniquet is applied to the extremities There was also roentgenographic evidence of narrowing of the transverse cardiac diameter upon the application of high mask pressures

Due to bronchial constriction the expiratory phase in asthmatic dyspnea is prolonged In obstructive dyspnea the intrapleural negative pressure is increased during inspiration When air or oxygen mixtures are breathed under positive pressures the abnormally elevated negative intrapleural pressure is diminished and the dyspnea is alleviated Barach[27] pointed out that nature provides a helpful mechanism in the expiratory grunt of the patient with lobar pneumonia and in the pursed lips of the asthmatic patient during expiration both spontaneously providing positive pressure

Using helium oxygen mixtures the patient can be treated for as many days as necessary in either the hood apparatus or positive pressure mask with proper humidification however the hood apparatus is better tolerated Therapy should be intermittent and generally for not more than one out of every four hours as the patient may find longer periods exhausting When the need for positive pressure no longer exists the mask can be used without employing the metered disk for positive pressure and the desired percentages of oxygen can be given or the patient may be transferred to a tent if this is considered more desirable In patients with underlying severe emphysema or cerebral arteriosclerosis the percentages of oxygen should be gradually lowered before the complete cessation of treatment in order to prevent the occurrence of cerebral and cardio respiratory symptoms which may follow the sudden cessation of oxygen therapy

Generally, positive pressures of 2 to 6 cm of water are sufficient for preventing or treating pulmonary edema and status asthmaticus Pressures above 6 cm may diminish the return flow of blood to the right side of the heart In some cases I have employed higher pressures for short periods If low pressures are used beginning with a pressure of 2 cm of water and cautiously increasing it as needed no difficulty need be encountered

In employing positive pressure therapy certain clinical observations are worthy of mention Many patients find such therapy tiring when the mask is used and an occasional critically ill patient at first becomes alarmed and confused at the increased resistance in the expiratory phase Reassurance and frequent rest periods can largely overcome this apprehension When the hood is employed the positive pressure is effective in both inspiration and expiration and these difficulties do not exist In the desperately ill patient Wangensteen drainage with a double lumen tube for feeding and decompression may be used in conjunction with positive pressure whenever indicated The tube can be introduced either through the mask or the sleeve of the hood apparatus it adds materially to the care of the very sick patient We have not observed either gastric dilatation or abdominal distension as a result of positive pressure therapy We wish to stress once again that positive pressure therapy should be intermittent with rest periods of varying time depending upon the degree of underlying pulmonary edema The dyspneic patient is soon able to rest and sleep may follow Respiratory decompensation is thus prevented If therapy is continuous free productive coughing and free belching may be somewhat inhibited We have not observed any irreversible ill effects from such therapy when continued for as long as seven days

4 Carbon dioxide-Oxygen and Carbon dioxide-Helium Oxygen Mixtures

A dry irritating non productive or poorly productive cough is frequently encountered in asthmatic subjects Every attempt should be made to reduce the viscosity of the exudate by the use of expectorant drugs therapeutic aerosols carbon dioxide and oxygen mixtures or carbon dioxide and helium oxygen mixtures Expectorant therapy is discussed more fully in Chapter VIII

The principal purpose of carbon dioxide therapy is to stimulate the respiratory center An increase in the respiratory rate and in the depth of respirations characterizes effective therapy of this type Carbon dioxide may act by increasing the acidity or the carbon dioxide tension of the respiratory center Increase in the acidity of the blood flowing through the carotid body as well as low oxygen pressures in the carotid body also stimulate breathing In addition increase in the blood carbon dioxide leads to a shift in the oxygen dissociation curve of hemoglobin to the right thus allowing increased release of oxygen to hypoxic tissues it also dilates the cerebral vessels

Considerable controversy still exists concerning the over all value of carbon dioxide inhalation as an expectorant in pulmonary disease Alison[8] used inhalations of 5 per cent carbon dioxide with oxygen in some cases of incipient pneumonia and bronchitis in children He believed that the disease process was aborted by the removal of the mechanical blocking of the airways Campbell and Poulton[9] also encouraged the use of carbon dioxide and oxygen in the treatment of pneumonia Banyai[9, 10] employed inhalations of 10 per cent carbon dioxide in oxygen in cases of pulmonary tuberculosis and believed that this

form of therapy was superior to the use of expectorants for the management of strenuous exhaustive non productive cough (tussic insufficiency) He observed that the increase in respiratory rate attendant upon inhalation of carbon dioxide was usually followed by easier expectoration and decreased cough The sputum changed from heavy thick and tenacious to thin serous and watery Banyai and Cadden[11] confirmed the value of carbon dioxided inhalations as an expectorant in pulmonary tuberculosis They attributed its effectiveness to a powerful stimulating effect on respiration which reflects itself in stretching and dilatation of the bronchi powerful peristaltic movements of the bronchi and liquefaction of the exudate that stagnates in the bronchial tree They also stressed its contra indication in recent pulmonary hemorrhage in severe emphysema in extensive pulmonary fibrosis without atelectasis bronchiectasis or mucopurulent retention in the air passages in acute pleurisy with effusion and in hypertension

In their exhaustive studies on the influence of expectorants and gases on sputum and on the mucous membranes of the tracheobronchial tree Basch Holinger and Poncher[31,32] demonstrated that the addition of 5 to 10 per cent carbon dioxide to an oxygen mixture acts as an efficient expectorant by reaching the deeper obstructive type of secretion They noted that the sputum was liquefied to a greater degree by steam inhalations than by expectorant drugs Since the steam reduced the viscosity and the content of organic and inorganic substances in the sputum its action appeared to be one of simple dilution These authors regarded the inhalation of carbon dioxide as a new and most efficient expectorant which reduces the amount of sputum within the bronchial tree by stimulating resorption and rendering the remainder

more liquid so that it is coughed up more easily They concluded that the best regimen to clear the bronchial tree of its pathological secretions was a combination of carbon dioxide steam inhalations and expectorant drugs

Inhalations of carbon dioxide oxygen mixtures may be employed when more conservative measures have failed and if there are no contra indications (particularly pul monary emphysema or edema) to increasing the rate and depth of respirations for short periods of time If deep breathing is maintained for long periods of time the in creased negative intrapulmonary pressure may accelerate the formation of edema from the pulmonary capillaries I have found mixtures of 5 per cent carbon dioxide 20 per cent oxygen and 75 per cent helium of occasional value when employed to nebulize mixtures of 0 25 cc of 1 per cent neosynephrin with 0 50 cc of Vaponefrin or Isuprel 1 200 This mixture has generally been well tolerated Each treatment should take five to ten minutes and should be interrupted if the respirations become too strenuous The sputum is liquefied expectoration is facilitated and tenacious thick mucus plugs are often coughed up These inhalations are designed to clear the bronchial and bronchiolar pathways

5 The Use of Therapeutic Aerosols *(sympathomimetic amines and antibiotic agents)*

Aerosols are relatively stable suspensions of liquids or solids in air or oxygen The terms nebulization therapy and aerosol therapy may be used interchangeably Abramson[2] objects to the use of the term vaporization He points out that the term vapor designates the gaseous form which a solid or liquid takes when heated As the particles in this state are practically of a molecular size and are therefore about ten thousand times smaller than

the particles of therapeutic aerosols now in use he claims that this term has been frequently misused

Numerous factors are involved in the determination of aerosol retention in the respiratory tract and their diffusion into the blood stream [3,4] The following are the more important factors the particle size distribution which depends essentially on the type of nebulizer and the precise technique employed the degree of deposition of the particles which depends for the most part upon impingement settling and diffusion by Brownian movement the pattern of the ventilatory curve particularly the respiratory rate the tidal air and the degree of bronchospasm which govern the penetration of the mist to the terminal bronchioles and alveoli aerodynamic factors such as turbulence and stream line flow and finally factors which may influence the size and life of the particles themselves namely the stability and surface tension of the aerosols

The selection of the proper nebulizer for the production of aerosols is of primary importance [2] True nebulizers differ from atomizers in that they are constructed with a baffle which removes from the mist the large particles which cannot penetrate the lower respiratory tract and which on impinging there may irritate the patient s tongue and throat The majority of the nebulizers which are commercially available are really atomizers

The exact particle size distribution of the aerosol governs the degree of retention and the site of deposition Findeisen[19] has demonstrated that particles of three micra radius and larger will undoubtedly be deposited completely on the trachea the bronchi the bronchioles and the alveolar ducts Impingement and sedimentation are the important mechanisms of deposition of these aerosols Particles of 1 micron radius and more are retained by the lungs to the extent of 97 per cent with only 3 per cent

recovered on expiration those of 0 3 micron are absorbed to the extent of only 35 per cent with 65 per cent recover on expiration Thus by the control of the particle size wide range of deposition distributions can be predicted These observations of Findeisen were confirmed by the experimental work of Van Wijk and Patterson[182] who demonstrated that from 63 to 96 per cent of solid particle of 0 6 to 2 0 micra radii were retained by the lungs Although they penetrate to the alveoli by Brownian move ment particles less than 0 4 micron in radius were retained only to the extent of about 30 per cent

These studies stress two important facts 1) larger parti cles such as those produced by most commercial nebu lizers tend to be deposited on the tongue pharynx and larynx and do not reach the bronchioles or alveoli and 2) particles much smaller in size tend to be exhaled rather than deposited on the bronchopulmonary surface At some optimum size maximum alveolar deposition will occur[183]

One may occasionally take advantage of the fact that large particles are deposited high in the respiratory pas sages in the management of inflammatory disease of the trachea and larger bronchi

Nebulizers should be constructed with a suitable baffle to remove the large particles and insure a uniform de livery of small particles preferably with the majority of radii in the 0 5 to 2 0 micra range In this country most of the investigators interested in aerosol therapy have em ployed the Vaponefrin nebulizer (Fig 15) We have found it most satisfactory for the production of therapeutic aerosols for it produces a fine voluminous mist or smoke screen in which the majority of the particle radii average about 1 micron and are capable of penetrating the alveoli and remaining there

Abramson[2,4] stresses the importance of prolonging the



FIGURE 15[144]

1. Vaponefrin Aerosol Motor Unit (A.C. Current) which can be used interchangeably with each of the following apparatus
2. Nebulizer for conventional bronchodilator therapy
3. Rebreathing bag and nebulizer apparatus with Y tube for administration of antibiotic aerosols
4. Apparatus for sinus therapy, nasal attachment, trap for drainage and venturi tube for alternate positive and negative pressure

life of the inspired particles (stability) so that the lung will retain a high percentage of them. Penicillin and streptomycin aerosols are sufficiently stable and do not require the addition of glycerin. Most of the pharmaceutical preparations of the various epinephrine derivatives employed as aerosols contain up to 10 per cent glycerin which lowers the vapor pressure, stabilizes the mist, reduces local irritation and prevents the particles from rapidly diminishing in size after leaving the nebulizer. In 1940 Abramson[1] suggested that 10 to 50 per cent glycerin was more suitable for stabilizing the mist and that other substances such as urea, sugar and salts could be employed. All of these act

to stabilize the mist by lowering droplet vapor pressure

A second important factor which controls the particle size and persistence of aerosols is the surface tension of the droplet[4] Lowering of the surface tension may produce a different particle size distribution but the stability may also decrease if smaller particles are formed The effect of lowering the surface tension of the particles is the subject of considerable research in many laboratories

Inhalation of nebulized sprays of various therapeutic agents may be employed in the management of bronchial asthma for the relief of the troublesome cough as an aid to expectoration and for the control of infection The use of antibiotic aerosols for the control of infection will be discussed in Chapter IX I have found aerosols of the sympathomimetic drugs Vaponefrin (racemic epinephrine hydrochloride) and Isuprel (1 (3 4'Dihydroxyphenyl) 2 ispropylaminoethanol) hydrochloride 1 200 of particular value for the relaxation of bronchospasm As little as approximately 0 05 to 0 10 cc of one of these solutions nebulized by three to six compressions of a hand bulb may abort or relieve a mild bronchospastic episode *It is* important that the patient actively inspire the aerosol and that he aid its deposition by holding his breath after inspiration for several seconds More severe bronchospasm may require 0 5 to 1 0 cc of the bronchodilator solution *nebulized by continuous flow of oxygen helium oxygen* or air pump (Fig 15) A Y tube or simple button like opening in the oxygen or air feed line allows interruption of aerosol production during expiration (Fig 15) Bronchodilator aerosols often convert a useless cough to a *productive one improve* the vital capacity and permit deeper respiration The effect of six inhalations of Vaponefrin aerosols on the ventilatory pattern of a subject with acute bronchial asthma is shown *in Figure 16 The*

striking improvement in the inspiratory and expiratory velocity speed and in the vital capacity is apparent. These inhalations should precede postural drainage and antibiotic aerosol therapy whenever these measures are performed. Postural drainage may then become effective by relieving the patient of retained inflammatory products

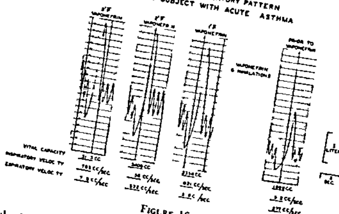


FIGURE 16

which previously could not be evacuated. Antibiotic aerosol therapy when indicated should follow postural drainage; evacuation of the bronchial secretions ensures avoidance of dilution of the antibiotic agent by the secretions and more efficient topical mucosal effect.

The combination of 0.5 cc. of Vaponefrin or Isuprel 1:200 and 0.5 cc. of 1 per cent neosynephrin is of particular value when there is bronchospasm accompanied by thick, tenacious sputum or a troublesome unproductive cough. Vaponefrin or Isuprel aerosol is also of value in preventing or relieving any allergic reaction which may

follow or accompany penicillin aerosol therapy Addition of neosynephrin produces particularly effective broncho-vasoconstriction which reduces mucosal congestion without the secondary vasodilatation which may occur with the use of topical epinephrine preparations alone It tends to diminish the secretions and to provide a more patent airway, although it is a poor bronchodilator Refractoriness and toxicity as observed with epinephrine and ephedrine do not develop In studying the effects of inhalations of neosynephrin in the ventilatory dynamics of the asthmatic subject, one can frequently demonstrate improvement in the vital capacity and increase in the inspiratory and expiratory velocity rates These effects, however, are not as great or as constant as those observed with inhalations of the epinephrine preparations or of Isuprel Occasionally epinephrine sensitivity may be restored more promptly with the use of neosynephrin aerosols alone As a rule the troublesome cough becomes easier and more productive after such therapy

Substituting helium and oxygen mixtures for oxygen is of further value if there is evidence of bronchial obstruction The helium oxygen mixture allows the nebulized solutions (Vaponefrin, Isuprel, neosynephrin penicillin or streptomycin) to pass through the contracted bronchi more freely and permits these preparations to act effectively on the mucosa and submucosa

The solutions are placed in the nebulizer which is connected by rubber tubing to the oxygen regulator or air pump The patient may use 0 5 to 1 0 cc of the bronchodilator preparation for a single dose Flows of 1 to 6 liters per minute are generally used and a single treatment takes about 20 minutes This may be repeated at intervals of three or four hours Prompt relief from the bronchospasm may be observed, the dyspnea usually subsides and the

vital capacity and the inspiratory and expiratory velocity rates quickly approach normal once again (Figs 2 and 16) This technique can be set up in the patient s home and the instructions are easily followed Many patients prefer such therapy before meals at bedtime and before undertaking any unusual exertion

The sympathomimetic aerosols should be employed only when specifically indicated and with well defined instruc tions to both the patient and the nurse The proper in halatory technique with the use of a small particle size nebulizer is most important The preparations should be clearly labeled by name and concentration and marked *for aerosol use only* On occasion they have accidentally been given parenterally with very disturbing side reac tions Excessive use should be firmly prohibited The pa tient must be instructed not to swallow saliva during treat ment and whenever possible to rinse his mouth thoroughly after each treatment Abdominal cramps may occur if the saliva is swallowed The saliva at times may be tinged pink With overdosage refractoriness and the usual side reactions observed with epinephrine may be seen Finally the patient should be taught to wait a full five minutes after one to three inhalations before repeating same

Prigal[8-33] has introduced the use of steam for the pro duction of medicated aerosols employing aminophyllin ammonium chloride penicillin solutions and other agents The results with aminophyllin and ammonium chloride aerosols were not impressive Our own protection studies[110] with aminophyllin aerosols demonstrate that this route is ineffective in preventing the effects of histamine and mecholyl induced bronchospasm and dyspnea in asthmatic subjects

CHAPTER VIII

BRONCHIAL EVACUATION—"CATHARSIS"

EVACUATION of the bronchi or what I term "bronchial catharsis" may be accomplished by physiologic mechanisms (Table 5) or therapeutic mechanisms (Table 6), the necessity for bronchial catharsis may be precluded by various preventive measures (Table 7) Catharsis, in the Freudian sense, too, may be of value in the management of the sick asthmatic In the physiologic sense, any

BRONCHIOLAR EVACUATION = CATHARSIS

I PHYSIOLOGIC MECHANISMS TO THIS END

FROM MACKLIN 114	FROM GUNN 94
1 COUGH REFLEX	—FUNCTIONS IN UPPER AIRWAYS
2 ACTION OF CILIA	—FUNCTIONS DOWN TO FINE BRONCHIOLES
3 PERISTALTOID WAVE MOTION	—FUNCTIONS TO EVACUATE ENTIRE TRACT

TABLE 5

II THERAPEUTIC MECHANISMS TO THIS END

1 EXPECTORANTS
   IODIDES AND SEDATIVE EXPECTORANTS
2 IPECAC
   TRACHEAL VOMITING
3 INHALATION THERAPY
   CO_2 O_2 HELIUM MIXTURES
   BRONCHODILATOR AEROSOLS
4 POSTURAL DRAINAGE
5 BRONCHOSCOPY
6 ENDOSCOPIC ASPIRATION
7 ENDOSCOPIC LAVAGE AND INSTILLATIONS OF
   CHEMOTHERAPEUTIC AND ANTIBIOTIC AGENTS

TABLE 6

III PREVENTIVE MEASURES

1 ELIMINATION OF AIR AND BLOOD-BORNE IRRITANTS
   ALLERGIC CLEANLINESS
   HYPOSENSITIZATION
   AIR FILTRATION
   INDUSTRIAL CONTACTS AEROSOL PROTECTION STUDIES

2 DIMINUTION OF AMOUNT OF MUCUS SECRETIONS
   AEROSOL THERAPY (NEOSYNEPHRIN)
   BELLADONNA ALKALOIDS OR SYNTHETIC EQUIVALENTS

3 BREATHING EXERCISES

TABLE 7

medication or procedure which will facilitate the removal of the retained impacted bronchial secretions is of great value in the treatment of this disease and may be life saving Bronchial catharsis may be accomplished in a variety of ways The expectorant drugs of which ipecac is probably the most effective may be considered bronchial evacuants

1 Expectorants

Expectorant drugs may play an important role in the management of the sick asthmatic The mucus in the bronchioles is usually tenacious and inspissated due largely to dehydration and long retention because of ineffectual cough The cough may become even more ineffective because of the impacted mucus and a state of tussic insufficiency develops Many expectorants and expectorant sedative mixtures have been employed the most common being the iodides and ammonium chloride We have never been certain of any definite benefit from inhalations of compound tincture of benzoin or the volatile oils of anise pine or eucalyptus Steam inhalations are preferable for their simple expectorant action Like wise mixtures employing creosote or guaiacol preparations

aqueous solutions of iodides are too irritating. The following mixture has proven very helpful in producing a thin watery, less tenacious secretion and in increasing the efficiency of cough and postural drainage.

Rx

Solution of Potassium Arsenite	10.00
Saturated Solution of Potassium Iodide	15.00
Sodium Phenobarbital	.30
Distilled water to make	240.00

Label: 4 cc t.i.d. p.c.

2. Ipecac

Ratner[12] has emphasized the value of induced vomiting following the administration of syrup of ipecac to infants and children. He attributes this to relief from bronchial obstruction rather than to relief from bronchiolar spasm. He divides asthma into two types: 1) that due to bronchial obstruction and 2) that due to bronchiolar spasm. The obstructive type is usually due to inhalants and when adrenalin fails to relieve the bronchiolar spasm then ipecac is indicated. The obstructive type is usually the cause of status asthmaticus. He states that according to Macklin three mechanisms have developed physiologically to free the respiratory tract from irritants and accumulated secretions: 1) the cough reflex, 2) the action of the cilia and 3) a wave motion said to resemble peristalsis (Table 5). These three factors often cooperate in the removal of foreign material such as exudates from the respiratory tract. According to Gunn[16] the cough reflex functions in the upper airway, the cilia act as far down as the fine bronchioles and the peristaltic movements evacuate the entire tract even including the airway terminals (Table 5). These activities may overlap. Remberg[14] described the effects of ipecac as tracheal

vomiting because of its resemblance to reverse peristalsis in the gastrointestinal tract By this process accumulation of thick inspissated mucus may be released and the bronchi evacuated

I have also found ipecac of value in the management of various stages of bronchial asthma in adults The patient *should be able to withstand the retching associated with* reverse peristalsis *Ipecac acts by substituting effective retching in place of ineffective coughing* It definitely is *worth a trial before attempting bronchoscopy* Once the tracheal vomiting has started positional drainage aids in eliminating the loosened secretions which under ordinary circumstances might not be released for days Relief is often striking particularly in the chronically ill and in patients with flabby musculature and low diaphragms The patient should be informed beforehand about the effects of this bronchial purge The syrup of ipecac may be administered in one two or three teaspoonful doses followed by a cup of lukewarm boiled water A smaller dose may be repeated in one hour if no effective emesis has occurred It can of course be repeated at any later date providing the indications suggest its use

3 Postural Drainage

Basch Holinger and Poncher[31, 32] have demonstrated that the mechanical drainage of the bronchial secretions is accomplished by the action of the cilia the respiratory movement the tissue squeeze of the cough reflex the cough itself and finally by expectoration

Physically able patients are urged to do as much of their coughing as possible in the position that will best utilize the force of gravity as an aid to drainage Many are able to avoid coughing if they empty their lungs thoroughly while they are in this position Generally

postural drainage is of little benefit to those with useless cough but it may be of considerable value in the management of the patient with accumulated secretions that are easily productive By placing the patient in a dependent position drainage of the involved part of the bronchial tree is facilitated Most patients soon learn the best position for raising the maximal amount of sputum The most dependent segments of the lung can be evacuated by having the patient kneel on the edge of the bed and place both elbows on a stool in order to have the thorax assume as nearly vertical a position as possible The patient should cough and expectorate for several minutes while in this position and drainage should be repeated before meals and bedtime or before each inhalation of penicillin aerosol during such a regime Asthmatic patients who have been unsuccessfully treated with penicillin aerosol may not have had adequate bronchiolar evacuation to permit satisfactory topical therapy Some asthmatic patients can empty their accumulated secretions in the morning and remain free of cough throughout the day

4 Endoscopic Therapy

Endoscopic therapy (a—bronchoscopy b—bronchoscopic aspiration c—endoscopic instillation of iodized penicillin and streptomycin suspensions and d—bronchial lavage) plays an important role in the prevention and relief of bronchial obstruction in the control of infection and in the restoration of the dynamic functions of the bronchi It thus may prevent and relieve the serious sequelae of obstructive emphysema segmental atelectasis and bronchiectasis

a Bronchoscopy—Bronchoscopy is a very valuable diagnostic and therapeutic procedure which is indicated whenever a harsh useless cough with dammed up secretions is

present and bronchospasm persists despite adequate physiologic management Thick tenacious and gelatinous sputum may be removed large amounts of the thinner secretions aspirated and bronchial drainage facilitated

Bronchoscopy permits direct inspection of the larger bronchi and their sub divisions The remaining bronchi can be explored with the aid of forceps and secretions aspirated for diagnostic purposes Bronchoscopy may be of particular value in the febrile state in the prevention or treatment of segmental atelectasis and in obstructive emphysema One of the most common and important causes of death in asthma is obstruction of the larger and smaller air passages by inspissation of tenacious secre tions which may form casts of the bronchial tree In status asthmaticus bronchoscopy generally reveals hemorrhagic swollen redundant mucosa with greatly narrowed bron chial diameters The bronchi constrict still further on expiration Lell[199] has described collapse of the posterior wall of the trachea during expiration in these patients Spectacular results may be observed following broncho scopic aspiration in such patients Finally endoscopic examination may reveal a remediable lesion such as a foreign body broncholithiasis a dilatable stenosis or a bronchial adenoma responsible for the asthmatoid wheeze simulating bronchial asthma

Partial bronchial obstruction occurs fairly frequently in patients with bronchial asthma and produces an obstruc tive emphysema— a functional blackout of the lung Clinically this is characterized by wheezing respiration commonly noted during the expiratory phase It can be detected by auscultation of the lung but is best heard with the stethoscope at the open mouth The common denomi nator in all types of wheezing respiration or asthmatoid wheezing is a narrowing of the airway During expira

tion the partially obstructed bronchus contracts and shortens the vibration of the outgoing air passing through this irregular lumen causes the characteristic expiratory wheezing sound. Because of this interference with the proper egress of air that portion of the lung beyond the obstruction contains a greater volume of trapped air than normally. Roentgenograms made at the end of full inspiration and forced expiration reveal the trapped air in the expiratory films; the inspiratory films remain the same. The diaphragm rises and the mediastinum shifts towards the affected side during inspiration.

It is important that the early stages of obstructive emphysema be promptly recognized so that development of complete bronchial obstruction can be prevented. When complete obstruction does occur, air does not get in or out and the residual air is slowly absorbed. We then have an organic blackout of the lung, technically termed obstructive atelectasis. The degree of obstruction depends principally upon the character and quantity of secretions, the adequacy of the cough reflex and the responsiveness of the bronchi to physiologic therapy. Accumulations of secretions in the bronchi beyond the point of obstruction may lead to a drowned lung. Bronchiectasis or so-called unresolved pneumonia may subsequently appear.

Having witnessed one death and two near fatalities with the use of pontocaine and cocaine sprays and instillations for local anesthesia in asthmatic subjects, I prefer deep surgical anesthesia for bronchoscopic aspiration. Divinyl ether (Vinethene) employed as a preliminary induction agent to ether permits a smooth and more rapid induction which is generally free of laryngeal irritation or spasm. The bronchoscopist or anesthetist should flood the airway with oxygen during anesthesia and bronchoscopy. With this technique intensive bronchoscopic aspiration in

cluding culture and stain of the secretions bronchial lavage with saline solution and instillation of solutions of penicillin and/or streptomycin in neosynephrin may prove of life saving value to the asthmatic subject

b **Bronchoscopic aspiration**—Aspiration of retained bronchial secretions should conclude bronchoscopic examination The secretions and material should be carefully preserved cultured and studied by special staining techniques for foreign bodies organisms and cells Clerf and his associates[50, 101] have done much to impress us with the value of bronschoscopy in bronchial asthma and with the importance of cytologic studies of the secretions obtained

Waldbott[197] vigorously stressed the value of bronchoscopic aspiration and lavage of the bronchial tree with saline solution in severe attacks Proper bronchoscopic aspiration is usually followed by marked subjective and objective improvement because it establishes drainage and rids the bronchi of accumulated secretions Removal of the bronchial obstruction may prevent or relieve the possible serious sequelae referred to previously

c **Endoscopic Instillation—(Intrabronchial and Intratracheal)**—The value of using solutions showing bactericidal or bacteriostatic activity for intrabronchial instillation or lavage has long been appreciated In recent years the employment of sulfonamides penicillin and streptomycin with more modern techniques of administration has been described for use in pulmonary suppurative disease[14, 83, 84]

Intrabronchial instillation—Although the introduction of radiopaque preparations into the tracheobronchial tree is essentially a diagnostic procedure it can likewise be utilized as an effective therapeutic medium[83, 84] The iodine in the oils is relatively inert and has little or no antiseptic

value However by mixing with the pocketed secretions the instillations mechanically help the patient in cleansing the larger and medium sized bronchial tubes thereby assisting expectoration and subsequent postural drainage Occasional intrabronchial instillations of suspensions or solutions of penicillin or streptomycin or both (depending upon the organisms present) in one of the iodine preparations (Pantopaque) may be of tremendous supplementary value to penicillin aerosol therapy

In several patients who were producing a great deal of purulent secretions bronchoscopic aspiration followed by bronchoscopic instillation of 250 000 units of penicillin and 0 5 grams (500 000 units) of streptomycin in 20 0 cc of Pantopaque was carried out just at the outset of penicillin aerosol therapy and on occasion repeated at weekly intervals if evidence of obstruction and or infection persisted We have occasionally mixed penicillin and streptomycin with 1 cc of 1 per cent neosynephrin and 0 20 cc of Vaponefrin or Isuprel 1 200 in 10 to 20 cc of Pantopaque The mixture was then instilled directly into both lungs through the bronschoscope This combination leads to dilution of the sputum and loss of its tenacious mucoid character thus lessening the necessary effort for expectoration Patients generally tolerate this procedure very well and feel considerably relieved after evacuating large amounts of secretions and inspissated pus that they previously had been unable to evacuate The neosynephrin acting as a bronchovasoconstrictor and the Vaponefrin or Isuprel acting as a bronchodilator provide a more patent airway The latter also prevents any bronchospasm that might occur following instrumentation and topical anesthesia The Pantopaque solution further helps in cleansing the bronchi and bronchioles of tenacious secretions which have become adherent to the mucosal

walls Furthermore since the solution is an aqueous one it does not cling to the bronchial mucosa and hence does not interfere with the action of the penicillin We have not observed any ill effects from penicillin saline Pantopaque instillations Moderate attacks of bronchial asthma were precipitated in two patients but they were quickly relieved by epinephrine injections Just what brought on the bronchospasm is questionable but it may have been due to Pontocaine sprays which preceded bronchoscopy

Intratracheal penicillin—Intratracheal penicillin has proven to be of greater value than intramuscular penicillin in the treatment of chronic bronchitis bronchiectasis and lung abscess We have been unable to demonstrate any penicillin in the sputum of patients with suppurative lung disease following intramuscular penicillin[83,84] On the other hand we have been able to demonstrate high sputum levels in the same patients following aerosol and endoscopic instillations In normal subjects we have also demonstrated adequate penicillin blood levels which persisted for a longer period than those following intramuscular injections These levels were highest when neosynephrin and Pantopaque were employed as diluents in place of saline[34,35,83,84]

The intratracheal technique is simpler than the intrabronchial one which requires bronchoscopy However I prefer the latter because diagnostic assistance and proper aspiration prior to each instillation can be obtained Cleaning the bronchi of tenacious secretions by aspiration further insures a concentrated topical effect for the antibiotic If atelectasis occurs this procedure should be repeated even more assiduously

d **Bronchial lavage**—Penicillin in normal saline solution sodium sulfathiazole solutions or physiologic saline solutions may be used for bronchial lavage As the best

preparation for lobectomy in patients with bronchiectasis Stevenson[15] has recommended bronchial irrigation with 20 to 30 cc of Bledsoe Fischer solution (sodium potassium and calcium chloride in distilled water) followed by postural drainage and elimination Penicillin was added to the solution as a final lavage if the bacteria involved were susceptible to penicillin Lavage was repeated two or three times at each treatment and three or more treatments were given weekly The patient was taught to perform the procedure without assistance Reactions though uncommon did occur

Although the principle of irrigation of an affected area may appear surgically sound it is not without danger for reinfection new infection or spread of infection to involved areas may occur Finally the possibility of sensitization to pontocaine (preliminary local anesthetic) with repeated usage should be borne in mind

CHAPTER IX

MANAGEMENT OF INFECTION IN BRONCHIAL ASTHMA

1 The Role of Infection in Bronchial Asthma

The role of pathogenic and non pathogenic bacteria fungi and viruses in bronchial asthma continues to be a controversial issue Whether or not infection acts as a primary excitant it is certain that infection plays a definite part in producing asthma Infection may act in any of the four following ways

a **Primary bacterial infections**—There is reason to believe that some cases of bronchial asthma are initiated by *bacterial infection* True *sensitization (immunologic)* similar to the mechanism in pulmonary tuberculosis although easy to invoke is difficult to prove with primary bacterial infection In suspected primary bacterial infections especially when definitively positive skin tests are obtained hyposensitization therapy employing a proper autogenous vaccine may be of considerable benefit *Stock mixed bacterial vaccines containing pneumococci* staphylococci streptococci and other organisms act as non specific therapy only *It is doubtful* whether immunological resistance to these organisms can be obtained from these mixed vaccines Nevertheless an occasional striking response may be noted following the use of stock vaccines prepared from virulent organisms To avoid danger of constitutional reactions the dose at the outset should be extremely small

b **Secondary respiratory infections**—Respiratory infection may occur secondarily in the patient with vasomotor

rhinitis allergic bronchitis or asthma Infection may begin in poorly aerated lung segments A bronchitis may be initiated and the cough and wheeze may persist The patient with vasomotor rhinitis (ragweed) for example, may start to sneeze in August and develop a wheeze shortly thereafter The symptoms may improve or subside in late October when the pollen count falls However a flare-up may occur in the fall and winter due to the prevalence of upper respiratory infections or due to house dust and fungi coincident with heating of homes (boxed in radiators and exposed piping systems) or to marked frequency of barometric and humidity changes The vicious cycle may continue or flare up again in the spring due to the effects of spring house-cleaning or tree pollens

c **Respiratory infections** may act as non specific trigger mechanisms—They may set off the loaded gun precipitating asthma in the sensitized individual Some alteration probably occurs in the immunological mechanism or respiratory mucous membrane so that the patient can no longer tolerate the extrinsic protein substance to which he is sensitive Wittich attributed this to a lowering (by bacterial infection) of the threshold for the entrance of the allergens It should be possible in these patients to observe the effects of the upper respiratory infection without the wheezing by effective allergic therapy removal of the offending allergen or by hyposensitization

d **Focal infections** of teeth tonsils lymphoid tissue of the naso-pharynx nasal polyps or sinuses rarely play an important primary role in bronchial asthma They should be dealt with surgically whenever proper indications are present but never during the pollen season Adenoid hypertrophy and infection nasal polyps and paranasal sinus disease are frequently related to the troublesome cough observed in patients with allergic bronchitis The

incidence of serious disabling chronic asthma is very high in these subjects Many allergists are of the opinion that an allergic reaction to bacteria or their products is the cause of the asthma and urge vaccine therapy Every effort should be made to maintain free drainage of the para nasal sinuses and freedom from infection in this group It is well recognized however that allergy is the dominant factor[97] in the maintenance of chronic para nasal sinus disease to treat the latter without regard to the underlying allergy is poor judgment

2 Control of Infection with Antibiotic Aerosols

The aim of antibiotic aerosol therapy[2, 8, 45, 110, 128, 1, 2] in the management of patients with bronchopulmonary infection is to produce as high a local concentration as possible in the sputum the tracheobronchial tree and the pulmonary tissues Attempts at control of the primary bronchial infection with intramuscular administration of penicillin and oral administration of sulfonamide drugs have proven disappointing

Every attempt should be made to identify the organisms from the nose throat and sputum before during and after therapy Whenever feasible sensitivity tests of the identified organisms to penicillin should be made at the outset and during and after treatment particularly if therapy is prolonged Although bacteria have been made resistant to penicillin in the test tube the development of clinical resistance has not become a major problem Once acquired however the resistance appears to be maintained indefinitely both in the laboratory cultures and in the body Fortunately any specific acquired resistance to sulfonamides penicillin or streptomycin does not affect the original susceptibility of the strain to one or more of the other drugs The precise mechanism (or site of action)

of each of these therapeutic agents is evidently different This makes it practical and logical to administer them in combination whenever feasible

Antibiotic aerosols have proven to be of great value in the management of infections of the laryngo-tracheobronchial tree The choice of drug depends on the predominating organisms their sensitivity and the patient s tolerance to the drug itself Penicillin is generally the primary drug employed streptomycin is added if gram-negative bacteria and bronchorrhea persist On occasion it may be advisable to start aerosol therapy with a combination of penicillin and streptomycin or to change from one antibiotic to another depending on subsequent bacteriologic findings It is hopeful that with the advent of new antibiotics more suitable preparations and combinations may be found although the problem of the development of resistant strains always must be kept in mind

In general we have found * * penicillin aerosol disappointing in patients with so-called chronic infectious bronchial asthma although striking improvement may occasionally be observed Most of our patients noted that they were able to raise sputum more easily while receiving the penicillin aerosol The danger of local or generalized allergic reaction to penicillin aerosol in the asthmatic group must never be overlooked Most of the local and urticarial reactions which we have observed when employing penicillin aerosol therapy have been in patients with bronchial asthma or bronchiectasis We have also on occasion noted the onset of mild bronchial asthma in patients receiving penicillin aerosol therapy for the management of chronic bronchitis emphysema or bronchiectasis The attacks however subsided promptly when inhalations of epinephrine were given after the penicillin aerosol had been discontinued

3 Technique and Dosage of Antibiotic Aerosol Therapy

Having once determined that antibiotic aerosol therapy is indicated it is important to employ the technique[35 374] best suited to the situation and to institute simultaneously supportive therapy that will restore and maintain physiologic function Antibiotic aerosol therapy can be administered to best advantage by the simple rebreathing technique (Fig 15) which should be modified according to *the patient s age and the nature of his illness Helium and* oxygen streams may be used in place of oxygen alone for those patients manifesting obstructive disease of the respiratory tract *This procedure is particularly valuable in patients* with segmental atelectatic lobes The antibiotic aerosols can be administered in tents hoods masks or tracheotomy openings For the treatment of patients with acute or chronic purulent sinus disease the aerosol should *be directed nasally with or without the technique of inter* mittent negative pressure

We generally employ 25 000 to 100 000 units of crystalline potassium penicillin in 1 0 to 3 0 of saline at three or four hour intervals depending upon the type and the degree of bronchopulmonary *infection* and the nursing care available If a streptomycin sensitive organism has been isolated 0 10 grams of streptomycin may be employed alone or in combination with the penicillin This therapy should be maintained for at least two days after all signs of infection have subsided At the end of each treatment at least one but preferably three rinses of 0 25 cc each of physiologic saline are added to the nebulizer and inhaled Any non toxic agent which lowers surface tension may be employed in place of the saline rinse e g several drops of 5 per cent alcohol or 0 05 per cent Duponol solution (E I *Du Pont de Nemours Company) This prevents wastage of* the drug from deposition in the nebulizer The time re

quired for each treatment ranges from 10 to 20 minutes depending upon the type of apparatus used and the rate of oxygen flow. Usually, the rebreathing Vapocillin apparatus requires flows of 6 or 7 liters of oxygen per minute. The new Vaponefrin motor blower air pump may be used in place of the oxygen (Fig. 15).

The best results can be obtained only if the bronchial passageways are patent. If there is evidence of bronchitis or if congestion of the bronchial mucosa is present, neosynephrin (0.25 to 1 per cent) is a better diluent than saline. When bronchospasm is present, we generally employ aerosols of Vaponefrin or Isuprel 1:200 preceding the neosynephrin penicillin aerosols. Generally, this therapy effects a freer and more productive cough and insures greater topical application of the penicillin resulting in higher and more prolonged blood levels. In some instances it is advisable to combine a mixture of 0.5 cc. of the bronchodilator drug and 0.5 cc. of 1 per cent neosynephrin as a solvent for the antibiotic drug.

Supportive therapy directed towards the restoration and maintenance of physiologic function is highly important in the management of sino-bronchial and bronchopulmonary disease associated with destruction, spasm or suppuration. Such therapy consists of the following: the maintenance of sino-bronchial tubal patency by the use of vasoconstrictor drugs, surgical roentgen ray, radium or radon therapy[80,81] for the eradication of hypertrophied lymphoid tissue of the nasopharynx (decreases the frequency and severity of asthmatic attacks in children), aspiration and drainage of sino-bronchial pathways, prevention and relief of atelectasis, management of bronchospasm with repeated bronchiolar[4,16] relaxation therapy, control of systemic infection with sulfonamides or parenteral penicillin, supplemental use of streptomycin aero-

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sols [12] and finally direct intratracheal or intrabronchial instillations of antibiotics for the management of persistent bronchopulmonary infection [83, 84]

The management of the patient with pulmonary emphysema is an example of the importance of supportive physiologically directed therapy in conjunction with the employment of antibiotic aerosols [174] Patients with chronic pulmonary emphysema generally present a history of cough progressive dyspnea even at rest loss of weight and weakness Clubbing of the fingers and cyanosis may be found in most of these patients and a small number have severe emphysematous blebs The lung has lost its elasticity the air sacs have become enlarged and the partitions between them have been destroyed Bronchiectasis and evidence of bronchospasm may also be found in many of these patients They are subject to recurrent infections of the respiratory tract and their pulmonary reserve diminishes with each episode The prognosis is generally poor and progressive respiratory failure ensues The patients can be made more comfortable with the use of 50 per cent concentrations of oxygen theophylline ethylene diamine and aerosolized bronchodilator drugs Supplemental elevation of the diaphragms by manual manipulation in expiration and the use of a proper abdominal belt may be of considerable value

Oral administration of sulfonamides and penicillin has proved of little value in our patients for the prevention of recurrent infection Furthermore these patients are generally not benefited by penicillin aerosol therapy alone Many are dyspneic and wheezy and have shallow respirations Poor mixing of tidal and resi air may prevent a proper and even distribution of t to distal bronchi and alveoli Rec ved improvement in of seven a se

monary emphysema when penicillin aerosol was added to the treatment described above In one of these patients diffuse emphysematous blebs and a minimal basal bronchiectasis complicated the picture In another patient a giant acquired cyst occupied the entire upper lobe of the right lung Five patients had uncomplicated pulmonary emphysema secondary to recurrent bronchial infections These patients were considerably improved after a course of penicillin aerosol therapy of from one to six weeks They had been treated with oxygen and bronchodilator drugs first but despite this more progressive dyspnea cyanosis and cough developed After administration of penicillin aerosol their vital capacities improved slightly and they have been able to maintain this improvement at home while continuing the previously outlined therapy These remissions have been striking though probably temporary

Patients with severe pulmonary emphysema who have failed to improve with a course of therapy employing the principles outlined should receive a course of penicillin aerosol therapy

4 Control of Para nasal Sinus Infection

Para nasal sinus disease may be responsible for re in fection and recurrence of cough and wheezing in patients with bronchial asthma Vigorous attempts at eradication of sinus disease should be made to prevent the irreparable sino-bronchitic syndrome which often follows in its wake Barach and his associates[23, 4] devised a simple venturi valve type of apparatus (Fig 15) for the administration of penicillin nasally which alternates positive and negative pressure with nebulization occurring during the positive phase Their patients have shown remarkable improvement in the condition of the sinuses after an intensive course of penicillin aerosol therapy Furthermore chronic

bronchitic disease has apparently disappeared in some cases with vigorous treatment of the (concurrent) para nasal sinusitis

We[174] have administered nasal penicillin therapy with alternating negative pressure just prior to penicillin aerosol via the pulmonary route Many of our patients with chronic sinusitis have previously had radical sinus operations with subsequent reinfection The technique of intermittent negative pressure and replacement with penicillin aerosol has not been on the whole as helpful in this group of patients as in those with uncomplicated acute sinusitis

Penicillin treatment of the para nasal sinuses (by displacement) through self induced intranasal negative pressure may be quite effective in certain patients However with the venturi technique for suction and replacement with penicillin aerosol considerably higher doses of penicillin may be employed without danger of damage to ciliary function It provides more uniform and diffuse mucosal application of the penicillin and adequate penicillin blood levels [3, 4] in about one half of the cases

Patients with chronic bronchial asthma and associated para nasal sinus disease derive considerable benefit from the supplemental use of antihistaminic drugs Hansel[9] has estimated that about *90 per cent of the patients who consult the otolaryngologist with the statement I have sinus trouble have allergy I generally advise (depending upon the individual s tolerance) 50 mgm of Benadryl Pyribenzamine or Pyrrolazote just before bed time and 25 mgm before breakfast* and again during the afternoon We[68] have found Hydryllin (Fig 8) a synergistically acting combination of aminophyllin and diphenhydramine effective in relieving para nasal obstruction and mild broncho spasm The dosage and choice of drug depends upon individual tolerance and needs Post nasal drip with secondary

cough is made minimal, nasal potency is restored and more restful sleep may follow

More recently we have supplemented the above therapy with the use of nasal sprays containing equal amounts of 1 percent Pyribenzamine and 1 percent neosynefrin This has proven quite effective in preventing the troublesome post nasal drip and cough which frequently precipitates asthmatic attacks

CHAPTER X

MISCELLANEOUS PROCEDURES EMPLOYED IN THE MANAGEMENT OF BRONCHIAL ASTHMA

1 Procedures Generally Not Recommended or of Lim e Value

Benefit has been described following a wide variety therapeutic procedures and in many instances specific has been claimed for these measures Very little if a benefit may be obtained from the following oral h mine or histaminase parenteral histamine or histam combined with protein (histamine azo protein) autol em therapy injections of calcium potassium sodium m nesium copper or gold injections of liver or vitam extracts injections of ovarian extracts pituitrin te terone peptone milk or venom the use of Ammi Vi na (Khellin) ethylene-disulfonate cholesterol nitrohd e chloric acid or potassium chloride roentgen therapy to th spleen pancreas or lungs and stringent dietotherapy s h as ketogenic diets

Notwithstanding the great skill of the modern thorac surgical team there appears to be little general end u m for the operative procedures designed for the purpose of in fluencing the neurogenic control of the bronchioles or chemical secretions Many surgeons recommend the re moval of the sympathetic stellate ganglia and the secon third and fourth thoracic ganglia if a preliminary g lion block yields good results Others recommend re e tion of the posterior pulmonary plexus (bilateral) Th responsiveness of asthmatic subjects to mecholyl may s n

as a possible guide for the pre operative evaluation of this procedure Recently, there has been an increased interest in the simpler procedures designed to block vagal influences, such as novocaine injection to the vagal fibres in the mastoid region [100] Occasionally troublesome coughing paroxysms have been stopped in this manner However the incidence of recurrence of bronchial asthma even in carefully selected cases is too high to warrant the more extensive surgical procedures

2 Procedures That May Be of Value

a **Psychotherapy**—The interrelationships of psychiatric phenomena with allergic reactions continue to stimulate considerable interest and discussion Emotional difficulties occur in many patients with bronchial asthma just as they do in patients with other medical illnesses Specific emotional factors and non specific factors, such as fatigue or infection can precipitate modify or inhibit attacks of bronchial asthma These factors appear largely as precipitating or ameliorating influences which disturb the delicate allergic threshold Curiously enough the patient with asthma shows remarkable variations in his reactions to these influences as well as to his allergens At times he can expose himself with relative impunity to a variety of sensitizing factors (foods danders and pollens) as well as to atmospheric changes and emotional disturbances without untoward results His psychobiologic adjustment may be maintained until a combination of factors disturb it An example of this may be observed in children with food sensitivities who develop asthma in their homes on exposure to certain foods, but are able to eat these same foods without ill effect when at camp nursing homes or visiting relatives where they are temporarily away from a tense atmosphere This would suggest an interrelationship be

tween the allergic state and emotional influences the exact nature of which is difficult to delineate

Another school of thought would establish a definite asthmatic (constitutional) personality or profile (more than normally intelligent over anxious insecure or lacking self confidence) as a result of the conversion of various psy chological conflicts into somatic symptoms This is es pecially true in children who appear to suffer from a deep seated insecurity and a more or less intense need for parental love and protection [149] Tension seems to be the connecting link between these conflicts and the asthma When pent up thwarted or frustrated these patients easily develop asthmatic attacks when free and relaxed they can better tolerate specific and non specific stimuli The attack of asthma itself further creates a vicious cycle resulting in loss of confidence interference with self expression greater frustration and more tension

The psychoanalytic school has helped to clarify the relationship of emotional disturbances to changes in body function Followers of this school of therapy generally regard the asthmatic paroxysm as having a symbolic mean ing French and Alexander[80, 81] have propounded the thesis that the asthmatic attack is the equivalent of a suppressed cry The asthmatic patient they feel is one who has been frustrated in his affections in early life and has been for bidden to cry crying being the infant s natural call for sympathy These authors state that asthmatic attacks tend to be precipitated by situations that threaten to separate the patient from his mother or some mother figure The separation feared may be an active physical separation but more frequently it is deeply repressed fear of es trangement from the parental figure due to some thought or temptation (sexual) to which the patient is exposed It is this temptation rather than the gratification which

usually precipitates the asthmatic attack.

Michaels,[33] in a provocative paper, suggested that just as there is regression in psychologic reactions, there may be regression in somatic visceral functions. He also presented the conception that the somatic components of the psychosomatic symptoms in the adult may resemble the physiological states of infancy either as an exaggeration or an accentuation. In a discussion with the author, he further proposed the hypothesis that in addition to the psychological meaning of the asthmatic attack, the asthmatic paroxysms from a biological point of view may represent a regression in the physiological reactions of the respiratory system. In his above mentioned paper he called attention to the increased tendency toward spasm in infancy as manifested in laryngeal spasm, stridor, sneezing and wheezing.

An emotional disturbance can rarely be proven the responsible primary etiologic agent in the pathogenesis of bronchial asthma. However, the emotional disturbance renders the patient more sensitive to the various factors which produce the attack and vice versa. It is desirable that the attending physician try to understand his patient and carefully study the various components in his life. Rapport should develop between the patient and his physician and the former's conflicts should be explored. This process of mental catharsis may preclude the need for bronchial catharsis at a later date.

In the case of children the problem requires even more attention. The asthmatic paroxysm is a frightening experience for the child and the parent. The child with asthma may often live in an environment of over protection and apprehension. Fastidious detail is placed on all of the child's vegetative functions. He is forbidden to participate in normal play and social activities. Limiting the child's activi-

ties actually may result in his own withdrawal from reality He is treated as if he were an infant with respect to food clothes and bodily functions indeed to the point of being wrapped in cotton wool The child soon wants to be protected and the parent out of a sense of guilt or for other reasons over protects him and a vicious cycle is thus established

Therapy in such cases is difficult because of the dis turbed parent child relationship The parents particularly the mother need most of the immediate help The child can also benefit from psychotherapy The term bronchial asthma should not connote fear however its seriousness should never be discussed in range of the child s hearing Likewise the comparative well being of other children should not be discussed in his presence This occurs too frequently during the first interview and one can sense the child s resentment He may conclude erroneously that I must be different weak and inferior Frequently the great emotional and financial strain the parents have been under is discussed in the child s presence Proper guidance should help direct the child to become more independent so that he can learn to stand on his own feet Situations capable of producing the extremes of suppressed rage and explosive behavior should be averted Whenever possible attendance at school homes and camps away from home should be encouraged for the incidence of attacks is re markably low in such friendly surroundings In due time proper explanations of the relationship of his environ ment and emotions to his disease can be made The child may then learn how to control the attacks he is unable to entirely prevent through understanding the precipi tating factors (physical and emotional) above all he may learn how to be happy in spite of having been born with an allergic diathesis

Unfortunately the physician as well as the family may unwittingly traumatize the patient by stressing the organic aspects of his bronchial asthma. The child soon feels that there is something physically wrong with his lungs. This situation is analogous to the announcement by the physician of the presence of a "functional heart murmur." The iatrogenic influence of the physician soon becomes felt and the asthmatic patient may then be said to have iatrogenic lung disease. The fear of such a pronouncement is frequently expressed by the adult patient who upon being told that he has bronchial asthma queries, "Well, doesn't that affect just my tubes but not my lungs?"

Probably all patients with bronchial asthma have emotional components. The relative proportion of allergy and emotional conflicts in the patient with bronchial asthma is difficult to determine. When the conflicts seem less the patient can be treated by his physician; where they are preponderant psychiatric evaluation should be advised. Certain knowledge may aid the physician in determining the type of psychiatric care that may be necessary. The age of onset is important as with other psychosomatic conditions. The younger the person the greater the likelihood of conflicts becoming more deeply embedded in the character structure. The patient may make use of his illness to gain or avoid certain things (secondary gain in illness). The very active person will fight invalidism and inactivity. The physician should first try to determine in what sphere of activity (family, spouse, children, work, society, school, etc.) the patient's asthma interferes most. He then should try to bring about a fair adjustment to present reality. The physician must distinguish symptomatic, supportive and limited goal psychotherapy from psychoanalysis, which consists of intensive therapy aimed to solve basic conflicts.

and lead to personality changes Properly directed allergic and physiologic therapy by lowering the incidence of asthmatic paroxysms may protect the individual from the reflex effects of neuro psychiatric factors which persist Finally it is much better for the attending physician to act in as human and kindly manner as possible and not attempt to deal psychologically with the emotional con fusion of the patient unless he has been especially trained to do so

There has been considerable interest in the use of shock therapy (insulin hypoglycemia and electro shock) for the management of the asthmatic patient I have had no per sonal experience with the first method Three of my patients however have been treated with electro shock therapy These patients were in the fifth to sixth decades of life had severe disabling chronic bronchial asthma and presented definite evidence of depression anxiety excitement or involutional changes The results were striking A remission which lasted for several months with subsequent development of a milder type of asthma was observed in two of the patients Treatment of the third patient resulted in a remarkable remission which has continued for five years This patient had chronic disabling bronchial asthma for more than 30 years with out evidence of any definite extrinsic allergens Physical and psychic factors usually ushered in her attacks She required three courses of electro shock therapy (five three and two convulsions respectively) over a period of eight weeks Her personality changed from that of a woman who was at times difficult doubtful despondent excited aggressive depressed and constantly concerned about her sneezing breathing and wheezing to a calm woman reassured and anxious to rid herself of an accumulation of syringes equipment and medications of a life time of

chronic invalidism Shock therapy in these patients helped to restore the psychobiologic equilibrium which then permitted the patient to better manage the underlying allergic state This type of therapy should not be recommended for the patient's asthma but rather for the personality disorder

b Climatotherapy—Climatic changes are available to only relatively few asthmatic sufferers and the physician should hesitate to urge such a program without carefully considering the many factors involved [37] Spa therapy and climatic changes occasionally afford help which may be attributed to a psychotherapeutic basis rather than to allergic cleanliness Separation from the mother figure mate business associate or other disturbing emotional influences when tempered by an enjoyable climate and refuge frequently brings relief from asthmatic paroxysms There is no general agreement as to what produces the improvement when a patient changes climate The progress of the disease may be influenced by many physical factors such as range of temperature and barometric pressure changes humidity wind variability proximity to the seashore sunshine altitude and other factors

Actual trial residence for at least one year may be the only certain answer However a few rules should be followed The patient with emphysema or co existing heart disease should not be sent to altitudes above 4 000 feet Those with troublesome bronchitis and considerable sputum may prefer the dry warm and generally calm climate of Southern California or Southern Arizona (Tucson or Phoenix) Those who are allergic to molds will probably have fewer symptoms in the dry climates The dry climate on the other hand may be responsible for retention of mucus or obstructive phenomena Those with scant and viscid sputum may fare better in the warm

moist climate of Georgia Florida or along the Gulf Coast These climates and regions are believed to favorably influence infectious respiratory processes Damp humid weather and especially fog are generally not well tolerated by most asthmatics Sudden temperature and barometic changes and electrical storms are likely to be followed by atmospheric changes which may precipitate attacks Atmospheres containing soot fumes and other chemical or mechanical irritants may also be precipitating factors and these should be avoided in making any changes

If pollen allergy is of major importance Southern California (Los Angeles Pasadena or San Diego) should be satisfactory California and all parts west of the Rockies are said to be practically free from ragweed and there is little ragweed pollen in parts of Florida Sufferers from grass pollen are less fortunate and probably will have symptoms in almost any part of the United States Those sensitive to tree pollens need only avoid the specific tree or trees responsible The foliage of the Southwest is quite different from that of the East and the pollen season lasts considerably longer (nine to 10 months) [157] Those sensitive to Bermuda grass and dust may fare poorly in certain sections of the Southwest Temporary relief from the irritation of pollen responsible for asthma can be found at seashore resorts on the West Coast and mountain resorts in New England particularly the area surrounding Bethlehem (New Hampshire) the Adirondacks Presque Isle (Maine) Isle Royale (Michigan) and Reno (Nevada) All of these places have low pollen indices[74] (maximum pollen concentration in the air) It is well to remember however that a resort area which would make a good haven because of its own low index may have higher indices because prevailing winds sweep in the pollen from the vast ragweed crop that thrives in the Midwestern States Furthermore a drop or sudden changes in barometric pressure

during the period when the pollen concentration in the air is low may precipitate bronchial asthma in seasonal asthmatic sufferers. An effective and enjoyable way to escape pollen is to take a cruise. Caribbean and South American cruises are favored by many.

Above all the physician should make certain that he is not sending his patient to a new climate containing allergens (pollens then in season) to which the patient is either already sensitive or to which he may become sensitive. Unfortunately the allergic subject has the inherent capacity for becoming increasingly sensitive to an ever widening list of agents.

c. **Therapeutic (Controlled) Hyperpyrexia**—The use of hyperpyrexia is based upon the fact that prolonged remissions in bronchial asthma may frequently follow febrile illnesses. Hyperthermia may be induced directly by employing intravenous typhoid vaccine or indirectly by the heat cabinet. We have on occasion employed the former method in seriously ill patients in status asthmaticus who were apparently non responsive to therapy. In [illegible] stances remission usually followed one or more [illegible] therapy while the recurring asthmatic crises [illegible] less severe and spaced at longer intervals [illegible] the patients more amenable to therapy. The me[illegible] this non specific improvement is not clear. [illegible] such as active participation of the cells in [illegible] chemical response or environmental (chemical [illegible] the autonomic nervous centers may play a role [illegible] be treated with hyperpyrexia should be careful[illegible] there are numerous contra indications to it [illegible] which are advanced cardio renal vascular d[illegible] pulmonary tuberculosis or pronounced deb[illegible] more administration of intravenous typhoid [illegible] on rare occasions be accompanied by se[illegible] states

I have employed a technique which is a modification of Solomon and Somkin s method [78] for obtaining sustained controlled hyperthermia with intravenous triple typhoid vaccine The details of the procedure and the usual reac tions therefrom should be explained to the patient Sodium phenobarbital 0 2 gm s c may be administered one hour before starting the intravenous infusion If there is no history or suspicion of aspirin sensitivity 0 65 gm of aspirin may be given forty five minutes later this *tends to minimize the subjective grippe like complaints* and chills that may follow The rectal temperature pulse and blood pressure should be recorded at fifteen minute intervals

Two infusion bottles (clearly labeled I and II) contain ing respectively 1 liter of 5 per cent glucose in isotonic sodium chloride and 1 liter of 5 per cent glucose in dis tilled water with 0 1 cc of triple typhoid vaccine (approxi mately 1 000 million typhoid bacilli per 1 cc) added are suspended from a clysis stand The respective rubber tub ings are connected by a Y tube to the intravenous needle Separate clamps on the rubber tubing should be used to regulate accurately the flow from the Murphy drip attachments to each flask

To insure proper hydration the patient first receives 500 cc from the glucose saline flask (I) at the rate of 90 drops per minute When completed the tube from this *flask is clamped off and the flow from the typhoid* infusion flask (II) is permitted to run at a rate of 40 to 60 drops per minute This is continued until a temperature plateau between *102° to 104° F* is *reached This temperature* is maintained for three to five hours by adjusting the flows from the respective flasks This can be controlled very simply with a little *experience If this temperature range* cannot be reached the typhoid dose may be altered by

increments of 0.1 cc. Many patients require as much as 0.3 cc of typhoid vaccine per liter of solution to obtain this goal. Generally two to four courses of therapy are sufficient to obtain a remission. The course may be repeated at two to three day intervals. Nasal catheter oxygen may be administered simultaneously to patients demonstrating the effects of severe chronic fatigue or hypoxia.

d. Breathing Exercises.—The purpose of these exercises is to re-establish the upward movement of the diaphragm and the bucket-handle movement of the lower ribs; they should also establish the habit of proper breathing and ultimately should render the rigid thorax more elastic. To become thoroughly adept at these exercises the patient should be under the guidance of a physical therapist. Supplemental passive massage, rhythmic compressions of the thorax and regulated gymnastics should be carried out. The tolerance for these procedures must be predetermined and the exercises increased as the patient's respiratory pattern improves. This type of therapy should be continued for a period of months or even years. This program can be of great value both to the young asthmatic and to patients with established emphysema; however, the results will vary. The routine described below may be a valuable measure in preventing the development of obstructive emphysema.

A detailed analysis of various series of exercises may be found in Delano's[11] or Gay's[45] book. Unfortunately, the need for proper supervision permits but a few patients to follow such a series to completion. The simpler procedure of attempting to elevate the diaphragm manually and at the same time pushing the lower ribs outward may give temporary relief by alleviating the over-distention of the lung. The patient should be instructed to place the palmar surface of both hands just below the ribs and

during the end of expiration to apply firm and increasing pressure upward to elevate the diaphragm and move the lower ribs outwards The patient may also purse his lips during the expiratory phase to produce a gentle back pressure in the tracheobronchial tree[20] This simple form of positive pressure therapy may further relieve the underlying bronchospasm These exercises should be done in the morning mid afternoon and at night Generally six to 12 such exercises spread over a period of several minutes are sufficient they should never be done to the point of fatigue On occasion temporary relief from the dyspnea due to obstructive emphysema may take place when the exercises are performed at the bedside by the physician while the patient is in the sitting position Periodic forceful sniffing may also produce some downward motion of the diaphragm The patient should be encouraged to apply a proper fitting abdominal belt (emphysema belt) following these exercises this helps to keep the diaphragm elevated Another modification consists of performing the breathing exercises with the emphysema belt in place and tightening it during expiration

Improvement in the vital capacity and decrease in the expiratory time may be observed after each complete series of exercises These exercises may act by increasing expiratory force and thus reducing lung volume This effect can be potentiated by preceding the exercises with three hand bulb inhalations of nebulized bronchodilator aerosols The improvement in vital capacity albeit brief may be prolonged by the administration of aminophyllin 0 3 to 0 75 gm administered rectally one half hour prior to the inhalation exercises In less severe cases aminophyllin preferably combined with ephedrine sulphate and phenobarbital may be given orally The improvement is most marked in the patients with emphysema

REFERENCES

1 Abramson H A Improved Inhalation Therapy of Asthma *Arch Phys Therapy 21* 612 1940
2 Abramson H A Combined Penicillin and Hydrogen Peroxide Aerosol Therapy in Lung Infections Preliminary Report *Ann Allergy, 4* 199 1946
3 Abramson H A and Demerec M Method for Experimental Control of Particle Size of Therapeutic Aerosols *J Allergy 16* 184 1945
4 Abramson H A Principles and Practice of Aerosol Therapy of Lungs and Bronchi *Ann Allergy 4* 440 1946
5 Alexander H L Johnson M C and Bukantz S C Studies on Correlation Between Symptoms of Ragweed Hay Fever and Titer of Thermostable Antibody *J Allergy 19* 1 1948
6 Alison J F Carbon Dioxide in Treatment of Acute Bronchitis and Early Pneumonia *South M J 25* 386 1932
7 Applebaum I L Cerebrovascular Accidents Following Epinephrine Injections Report of two cases *J Allergy 15* 392 1944
8 Baldwin E Bronchial Asthma Combined Staff Clinics of the College of Physicians and Surgeons Columbia University *Am J Med 1* 193 1946
9 Banyai A L Carbon Dioxide Inhalation in Pulmonary Tuberculosis *Am Rev Tuberc 30* 612 1934
10 Banyai A L Fifteen Years Experience with Carbon Dioxide in Management of Cough *Dis of Chest 13* 1 1947
11 Banyai A L and Cadden A V Carbon Dioxide by Inhalation in Management of Cough With Observations on its Effects upon Respiration in Pulmonary Tuberculosis *Brit J Tuberc 38* 111 1944
12 Barach A L The Use of Helium as New Therapeutic Gas *Proc Soc Exper Biol & Med 32* 462 1934
13 Barach A L Use of Helium as New Therapeutic Gas *Anesth & Analg 14* 210 1935
14 Barach A L Use of Helium in Treatment of Asthma and Obstructive Lesions in Larynx and Trachea *Ann Int Med 9* 739 1935
15 Barach A L Effects of Inhalation of Helium Mixed with Oxygen on Mechanics of Respiration *J Clin Investigation 15* 47 1936
16 Barach A L Physiological Methods in Diagnosis and Treatment of Asthma and Emphysema *Ann Int Med 12* 454 1938

17 Barach A L Obstructive Lesions in the Trachea and Bronchi In *Modern Medical Therapy in General Practice* Vol 3 3661 pp Baltimore Williams and Wilkins Company 1940 Pp 2472 2476

18 Barach A L Repeated Bronchial Relaxation in Treatment of Intractable Asthma *J Allergy 14* 296 1943

19 Barach A L *Physiologically Directed Therapy in Treatment* of Intractable Bronchial Asthma *Bull New York Acad Med 20* 538 1944

20 Barach A L *Physiologic Therapy in Respiratory Diseases* Second Edition Philadelphia J B Lippincott & Co 1948

21 Barach A L Rectal Instillation of Aminophylline in Intractable Asthma *J A M A 128* 589 1945

22 Barach A L Treatment of Intractable Asthma *J Allergy 17* 352 1946

23 Barach A L Garthwaite B and Rule C Use of Penicillin Aerosol in Bronchopulmonary and Sinus Infections *New York State J Med 46* 1703 1946

24 Barach A L Garthwaite B Rule C Talbot T R Jr Kernan J D Babcock J and Brown G Penicillin Aerosol and Negative Pressure in Treatment of Sinusitis *Am J Med 1* 268 1946

25 Barach A L Martin J and Eckman M Positive Pressure Respiration and its Application to the Treatment of Acute Pulmonary Edema and Respiratory Obstruction *J Clin Investigation 16* 664 1937

26 Barach A L Martin J and Eckman M Positive Pressure Respiration and its Application to Treatment of Acute Pulmonary Edema *Ann Int Med 12* 751 1938

27 Barach A L and Molomut N An Oxygen Mask Metered for Positive Pressure *Ann Int Med 17* 820 1942

28 Barach A L Silberstein F H Oppenheimer E T Hunter T and Soroka M Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma Chronic Bronchitis Bronchiectasis and Lung Abscess Preliminary Report *Ann Int Med 22* 485 1945

29 Barach A L and Swenson P C Effect of Breathing Gases Under Positive Pressure on Lumens of Small and Medium [illegible] 1939

30 B[illegible] cular Disease *J A M A 137* [illegible] 584 1948

31 Basch F I Holinger P H and Poncher H G Physical and Chemical Properties of Sputum *Influence of Drugs* Steam

Carbon Dioxide and Oxygen *Am J Dis Child* 62 1149 1941

32. Basch F P Holinger P H and Poncher H G Physical and Chemical Properties of Sputum Factors Determining Variations in Portions from Different Parts of Tracheobronchial Tree *Am J Dis Child* 62 981 1941

33. Beakey J F Bresnick E Levinson L and Segal M S Evaluation of Therapeutic Substances Employed for the Relief of Bronchospasm. 3 Anticholinergic Agents *Ann Allergy* 7 113 1949

34. Beakey J F Gaensler E and Segal M S The Pharmacodynamics of Pulmonary Absorption in Man 2 Influence of Various Diluents on Aerosol and Intratracheal Penicillin *Ann Int Med* 31 805 1949

35. Beakey J F Gaensler E and Segal M S A Comparative Study of Various Apparatus and Techniques for Aerosol Administration *Connecticut M J* 13 855 1949

36. Beecher H K Fatal Toxic Reactions Associated with Tribromethanol Anesthesia *J A M A* 111 122 1938

37. Bloomfield R A Lauson H D Cournand A Breed E S Richards D W Jr Recording of Right Heart Pressures in Normal Subjects and in Patients with Chronic Pulmonary Disease in Various Types of Cardiopulmonary Disease *J Clin Investigation* 25 639 1946

38. Boothby W M Mayo C W and Lovelace W R Oxygen and Oxygen and Helium Therapy Recent Advances *M Clin North America* 23 977 1939

39. Boothby W M Mayo C W and Lovelace W R One Hundred Per Cent Oxygen Indications for Its Use and Methods of Its Administration *J A M A* 113 477 1939

40. Boothby W M Mayo C W and Lovelace W R Jr Use of Oxygen and Oxygen Helium with Special Reference to Surgery *S Clin North America* 20 1107 1940

41. Bresnick E Beakey J F Levinson L and Segal M S Evaluation of Therapeutic Substances Employed for the Relief of Bronchospasm 5 Adrenergic Agents *J Clin Investigation* 28 1182 1949

42. Bresnick E Woodard W K and Sageman C B Fatal Reactions to Intravenous Administration of Aminophylline *J A M A* 136 397 1948

43. Brown E A The Use of Intravenous Ethyl Alcohol in the Treatment of Status Asthmaticus *Ann Allergy* 5 193 1947

44. Brown E A and Gillespie J D Round Table Discussion

Fall Graduate Instructional Course American College Al lergists Cincinnati Ohio (Nov) 1947
45 Bryson V, Sansome E and Laskin E Aerosolization of Peni cillin Solutions *Science 100* 33 1944
46 Burrage W S Recent Therapeutic Trends in Allergy *New England J Med*, *238* 181 1948
47 Burstein C L The Hazard of Paraldehyde Administration *J A M A*, *121* 187 1943
48 Campbell J M H and Poulton E P *Oxygen and Carbon Dioxide Therapy* 195 pp New York and London Oxford University Press 1934
49 Charlier R L Utilisation des Aérosols d Aleudrine pour le Traitement Prolongé de l Asthme Importance de la Rigueur dans l Application de cette Thérapeutique *Rev belge sc med 17* 108 1946
50 Clerf L H Bronchoscopy in Bronchopulmonary Disease *Modern Medicine 13* 53 60 1945
51 Clough G M Use of Helium *M J Australia* 2 400 1939
52 Cohen M B Bronchial Asthma Classification Based on Etiological and Pathological Factors *Ann Int Med*, *20* 590 1944
53 Colton W A and Ziskin T Heart in Bronchial Asthma *J Allergy 8* 347 1937
54 Cooke R A *Allergy in Theory and Practice* Chap 3 Phila delphia *W B Saunders XXV 1947 572 p*
55 Cooke R A The Immunology of Allergic Disease *Am J Med 3* 523 1947
56 Cournand A Recent Observations on Dynamics of Pulmonary Circulation *Bull New York Acad Med 23* 27 1947
57 Cournand A Richards D W Jr and Darling R C Graphic Tracings of Respiration in Study of Pulmonary Disease *Am Rev Tuberc 40* 487 1939
58 Cournand A Riley R L Breed E S Baldwin E deF and Richards D W Jr Measurement of Cardiac Output in Man Using Technique of Catheterization of Right Auricle or Ventricle *J Clin Investigation 24* 106 1945
59 Craige B Jr Fatal Bronchial Asthma Report of 7 Cases *Arch Int Med 67* 399 1941
60 Crowe S J Irradiation of Nasopharynx (Wherry Memorial Lecture) *Tr Am Acad Ophth 51* 29 1946
61 Crowe S J and Walzl E M Irradiation of Hyperplastic Lymphoid Tissue in Nasopharynx *J A M A*, *134* 124 1947
62 Curry J J Action of Histamine on Respiratory Tract in

Normal and Asthmatic Subjects *J Clin Investigation 25* 785 1946

63 Curry J J Effect of Antihistamine Substances and Other Drugs on Histamine Bronchoconstriction in Asthmatic Subjects *J Clin Investigation 25* 792 1946

64 Curry J J Comparative Action of Acetyl Beta Methylcholine and Histamine on the Respiratory Tract in Normals Patients with Hay Fever and Subjects with Bronchial Asthma *J Clin Investigation 26* 430 1947

65 Curry J J and Lowell F C Measurement of Vital Capacity in Asthmatic Subjects Receiving Histamine and Acetyl Beta Methylcholine A Clinical Study *J Allergy 19* 9 1948

66 Dale H H and Gaddum J H Reactions of Denervated Voluntary Muscle and Their Bearing on Mode of Action of Parasympathetic and Related Nerves *J Physiol 70* 109 1930

67 Dautrebande L Philippot E Charlier R Dumoulin E and Norgarède F Étude des Aérosols Médicamenteux chez l'homme Influence sur le degré d'efficacité de la respiration pulmonaire de médicaments dits bronchodilateurs et bronchoconstricteurs en inhalation *Presse méd 49* 1081 1941

68 Dautrebande L Philippot E Charlier R and Dumoulin E Aérosols Médicamenteux Essais de Traitement des États Asthmatiformes par Aérosols de Substances Pneumodilatrices et d'Autovaccins *Presse méd 50* 566 1942

69 Dautrebande L Philippot E and Charlier R Aérosols Médicamenteux Nouvelle Demonstration de leur Action Générale Étude expérimentale des aérosols de Carbaminocholine et d'Atropine *Presse méd 50* 398 1942

70 Dautrebande L *Therapeutic Aerosols Technique Physiology and Therapeutic Application* Paris Maison et Cie 1946

71 Delano S *Health and Rehabilitation Through Chest Training* New York The William Frederick Press 1947

72 Dublin L I Statistics of Bronchial Asthma Chapter III in the *Treatment of Bronchial Asthma* Derbes V J and Engelhardt H T Philadelphia Lippincott 1946

73 Dublin W B Faldes F J and Williams M M D Voice Changes with Mixture of Helium and Oxygen *Proc Staff Meet Mayo Clin 15* 586 1940

74 Durham Oren C Our National Parks as Ragweed Hay Fever Refuges *J A M A 138* 126 1948

75 Eckman M and Barach A L Inhalational Therapy Equipment *Mod Hosp 52* 78 1939

76 Evans J H The Rationale of Oxygen Dosage *Anesth and Analg 21* 35 1942

77 Eyermann C H Diagnosis and Treatment of Bronchial Asthma *Dis of Chest* 6 234 1940

78 Farrerons Co F J Histamine Sympathin Balance *Ann Allergy* 7 46 1949

79 Findeisen W Über das Absetzen kleiner in der Luft suspendierter Teilchen in der menschlichen Lunge bei der Atmung *Pflugers Arch f d gest Physiol* 236 367 1935

80 French T M Psychogenic Factors in Asthma *Am J Psychiat* 96 87 1939

81 French T M and Alexander F *Psychogenic Factors in Bronchial Asthma* Part 1 Psychosomatic Medicine Monographs Vol I Part II Psychosomatic Medicine Monographs Vol II 1 2

82 Fuchs A Interruption of Asthmatic Crisis by Tribromethanol (Avertin) *J Allergy* 8 310 1937

83 Gaensler E, Beakey J F and Segal M S The Pharmacodynamics of Pulmonary Absorption in Man I Aerosol and Intratracheal Penicillin *Ann Int Med* 31 582 1949

84 Gaensler E Beakey J F and Segal M S The Relative Effectiveness of Parenteral Intratracheal and Aerosol Penicillin in Chronic Suppurative Disease of the Lung *J Thoracic Surg* 18 546 1949

85 Gay L N *Diagnosis and Treatment of Bronchial Asthma* Baltimore Williams and Wilkins Co 1946

86 Godlowski Z Insulin Shock Treatment of Bronchial Asthma *Brit Med J* 1 717 1946

87 Goldsmith N Now Helium Saves Lives Mixture of Helium with Oxygen Is Beginning to be Used by Physicians to Tide Respiratory Cripple Cases Such as Chronic Asthmatics Over Their Crises *Scient Am* 160 153 1939

88 Goodall R J and Unger L Continuous Intravenous Aminophyllin Therapy in Status Asthmaticus *Ann Allergy* 5 196 1947

89 Graeser J B Inhalation Therapy of Bronchial Asthma *J A M A* 112 1223 1939

90 Graeser J B and Rowe A H Inhalation of Epinephrine for Relief of Asthmatic Symptoms *J Allergy* 6 415 1935

91 Graham J D P and Gurd M R Comparison of Epedrine and Eserine *J Pharmacol & Exper Therap* 72 48 1941

92 Greene J A Paul W D and Feller A E The Action of Theophylline with Ethylenediamine on Intrathecal and Venous Pressures in Cardiac Failure and on Bronchial Obstruction in Cardiac Failure and in Bronchial Asthma *J A M A* 109 1712 1937

93 Gregory J E and Rich A R Experimental Production of Anaphylactic Pulmonary Lesions with Basic Characteristics of Rheumatic Pneumonitis *Bull Johns Hopkins Hosp* 78 1 1946
94 Gunn J A Action of Expectorants *Brit M J* 2 972 1927
95 Gunn J A Pharmacological Actions and Therapeutic Uses of Some Compounds Related to Adrenaline (Oliver Sharpey lecture) *Brit M J* 2 155 1939
96 Hambourger W E Freese H B Winbury M M and Michiels P M Protective Action of Combinations of Diphenhydramine and Aminophyllin in Fatal Bronchospasm in Guinea Pigs Due to Mecholyl Aerosol *J Pharmacol and Exper Therap* 94 367 1948
97 Hansel F K Otolaryngologic Phases of Allergy Panel Discussion of the American College of Allergists, March 14 1948 at New York
98 Harkavy J Vascular Allergy in the Pathogenesis of Bronchial Asthma with Recurrent Pulmonary Infiltrations and Eosinophilic Polyserositis *J Allergy* 11 622 1940
99 Harkavy J Vascular Allergy Pathogenesis of Bronchial Asthma with Recurrent Pulmonary Infiltrations and Eosinophilic Polyserositis *Arch Int Med* 67 709 1941
100 Harken D Personal Communication
101 Herbut P A and Clerf L H Cytology of Bronchial Secretions Diagnostic Aid in Diagnosis of Pulmonary Tuberculosis *Am Rev Tuberc* 54 488 1946
102 Hill L W Food Sensitivity in 100 Asthmatic Children *New England J Med* 238 657 1948
103 Kabat E A Immunochemistry of Proteins *J Immunol* 47 513 1943
104 Kabat E A Quantitative Immunochemical Aspects of Some Allergic Reactions *Medicine* 3 535 1947
105 Kernan J D and Barach A L Role of Helium in Cases of Obstructive Lesions In Trachea and Larynx *Arch Otolaryng* 26 419 1937
106 LaDue J S in Derbes V J and Engelhardt H T *Treatment of Bronchial Asthma* Philadelphia J B Lippincott Co XI 166 1946
107 Lamson R W and Butt E M Fatal Asthma Clinical and Pathologic Consideration of 187 Cases *J A M A* 108 1843 1937
108 Lands A M Nash V L Dertinger B L Granger H R and McCarthy H M The Pharmacology of Compounds

Structurally Related to Hydroxytyramine *J Pharmacol & Exper Therap*, 92 369 1948

109 Lell W ... d Treatment of Al ... 43 49 1946

110 Levine, ... 'ronchial In fectio

111 Levinson L, Beakey, J F, Bresnick, E and Segal, M S Eval uation of Therapeutic Substances Employed for the Relief of Bronchospasm 2 Historical Development and Methods *Ann Allergy*, 6 705, 1948

112 Loveless, M H Immunological Studies of Pollenosis relation ship between thermostable antibody in circulation and clini cal immunity *J Immunol*, 47 165, 1943

113 Lowell F C *The Treatment of Bronchial Asthma* Address Delivered before the Mass Med Soc June 1948

114 Macklin C C Musculature of Bronchi and Lungs *Physiol Rev*, 9 1 1929

115 Marsh D F, Pelletier, M H and Ross C A The Compara tive Pharmacology of the N alkyl Arterenols *J Pharmacol & Exper Therap*, 92 108, 1948

116 Maytum C K Prickman, L E, and Boothby, W M The Use of Helium and Oxygen in the Treatment of Severe In tractable Asthma *Proc Staff Meet, Mayo Clin*, 10 788 1935

117 McMichael J Circulatory Failure Studied by Means of Venous Catheterization *Advances in Internal Medicine*, 2 61 New York Interscience Publishers, Inc, 1947

118 McMichael J Heart Failure of Pulmonary Origin *Edinburgh M J*, 55 65 1948

119 McMichael J and Sharpey Schafer, E P The Action of Intravenous Digoxin in Man *Quart J Med*, 13 123, 1944

120 Merrill G A Aminophylline Deaths *J A M A*, 123 1115 1943 (Correction *Ibid*, 124 250 1944)

121 Metz C W Wearner, A A and Evans A E Therapeutic Use of Helium, *South M J*, 32 35 1939

122 Meyer N E and Schotz, S Relief of Severe Intractable Bronchial Asthma with Cyclopropane Anesthesia Report of Case *J Allergy*, 10 239, 1939

123 Michaels J J A Psychiatric Adventure in Comparative Patho physiology of the Infant and Adult With Some Theoretical Suggestions in Regard to Regression in Somatic Visceral Functions *J Nerv Ment Dis*, 100 49 1944

124 Moll, H H Action of Parasympatheticmimetic Drugs in Asthma *Quart J Med*, 9 229, 1940

125 Moller K O Über die Behandlung der Akuten Adrenalinvergiftung mit Bericht uber einem Vergiftungsfall *Acta med Scandinav* 110 359 1942

126 Munch J C Gattone V H and Pratt H J Pressor Drugs Chemistry and Pharmacology of Analogue of Epinephrine *J Am Pharm A (Scient Ed)* 30 183 1941

127 Nathanson M H Pathology and Pharmacology of Cardiac Syncope and Sudden Death *Arch Int Med* 58 685 1936

128 Olsen A M Nebulized Penicillin Preliminary Report of its Role in Management of Surgical Bronchiectasis *Proc Staff Meet Mayo Clin* 20 184 1945

129 Olsen A M Nebulization Therapy in Bronchiectasis the Use of Penicillin and Streptomycin Aerosols *J A M A* 134 917 1947

130 Paul W D Heart in Bronchial Asthma *J Iowa M Soc* 25 643 1935

131 Peters G A and Silverman J J Role of Histamine and Acetylcholine in Mechanism of Heart Allergy Report of Studies on Soldier *Arch Int Med* 77 526 1946

132 Prigal S J Production of Aerosols from Medicated Solutions Combined Steam Generator and Aerosolizer *J A M A* 131 398 1946

133 Prigal S J Brooks A M and Harris R Treatment of Asthma by Inhalation of Aerosol of Aminophyllin *J Allergy* 18 16 1947

134 Proger S and Decaneas D J Some Further Observations on Parenteral Use of Cytochrome C with Special Reference to Cerebral Anoxia and Shock *Bull New England M Center* 7 149 1945

135 Proger S Decaneas D J and Schmidt G Some Observations on the Effect of Injected Cytochrome C in Animals *J Clin Investigation* 24 864 1945

136 Raab W Sudden Death of Young Athlete with Excessive Concentration of Epinephrine like Substances in Heart Muscle *Arch Path* 36 388 1943

137 Rackemann F M Studies in Asthma Clinical Survey of 1074 Patients with Asthma Followed for Two Years *J Lab Clin Med* 12 1185 1927

138 Rackemann F M The Use of Drugs in Asthma *J A M A* 114 1998 1940

139 Rackemann F M Deaths from Asthma *J Allergy* 15 219 1944

140 Rackemann F M A Working Classification of Asthma *Am J Med* 3 601 1947

141 Randolph T G Food Allergy *M Clin North America* *32* 245 1948
142 Ratner B Pediatric Approach to Management of Asthma in Childhood *New York State J Med* *47* 861 1947
143 Ratner B Management of the Asthmatic Attack in Childhood *M Clin North America* *31* 537 1947
144 Reinberg S A Roentgen ray Studies on Physiology and Pathology of Tracheobronchial Tree *Brit J Radiol* *30* 451 1925
145 Rich A R The Pathogenesis of Forms of Jaundice *Bull Johns Hopkins Hosp* *47* 338 1930
146 Rich A R Role of Hypersensitivity in Periarteritis Nodosa as Indicated By Seven Cases Developing During Serum Sickness and Sulfonamide Therapy *Bull Johns Hopkins Hosp* *71* 123 1942
147 Rich A R Role of Hypersensitivity in Pathogenesis of Rheumatic Fever and Periarteritis Nodosa (Lewis Linn McArthur lecture) *Proc Inst Med Chicago* *15* 270 1945
148 Richards D W Jr Barach A L and Cromwell H A Use of Vaporized Bronchodilator Solutions in Asthma and Emphysema Continuous Inhalation Method for Severe Asthmatic States *Am J M Sc* *199* 225 1940
149 Rogerson C H Psychological Factors in Asthma *Brit M J* *1* 406 1943
150 Rovenstine E A and Phelps M L Respiratory Obstruction from Bronchiolar Constriction During Cyclopropane Anesthesia *J Thoracic Surg* *11* 565 1942
151 Rowe A H Bronchial Asthma Its Diagnosis and Treatment *J A M A* *111* 1827 1938
152 Rowe A H *Elimination Diets and the Patients Allergies A Handbook of Allergy* Philadelphia Lea and Febiger 2 256 1944
153 Rubin E H *Diseases of the Chest with Emphasis on X ray Diagnosis the Principles of Surgical Treatment* by Morris Rubin Philadelphia W B Saunders Co VII 685 1947
154 Rubitsky H J Bresnick E Levinson L Risman G and Segal M S Parenteral and Aerosol Administration of Antihistaminic Agents in the Treatment of Severe Bronchial Asthma *New England J Med* *241* 853 1949
155 Salter H H *On Asthma Its Pathology and Treatment* London Churchill 2 464 1868
156 Schiller I W Colmes A and Davis D The Occurrence of Cor Pulmonale in Cases of Bronchial Asthma *New England J Med* *228* 113 1943

157 Schutzbank F B Climatotherapy in the Treatment of Allergic Diseases (Clinical Report J Allergy 19 244 1948
158 Schwartz A L Relief of Status Asthmaticus by Helium (Case Report) J Med 19 122 1938
159 Seegal B Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University Am J Med 1 190 1946
160 Segal M S Inhalational Therapy in Respiratory Disease Bull New England M Center 5 104 1943
161 Segal M S Inhalation Therapy in Treatment of Serious Respiratory Disease New England J Med 229 235 1943
162 Segal M S Medical Progress Inhalation Therapy New England J Med 230 456 1944 485 1944
163 Segal M S Advances in Inhalation Therapy with Particular Reference to Cardiorespiratory Disease Med 231 553 1944
164 Segal M S Progress in Inhalation Therapy New England J cine 34 63 1946
164a Segal M S Facts and Fancies in the Management of the Seriously Ill Patient with Bronchial Asthma Modern Medi 14 795 1948
165 Segal M S and Aisner M Management of Certain Aspects of Gas Poisoning with Particular Reference to Shock and Pulmonary Complications Dis of Chest 9 62 1947
166 Segal M S and Beakey J F The Use of Isuprel for the Management of Bronchial Asthma Ann Int Med 20 219 1944
167 Segal M S and Beakey J F Management of Bronchial Asthma The Use of 1 (3 4 Dihydroxyphenyl) 2 isopropylaminoethanol Bull New England Center
168 Segal M S Beakey J F Bresnick E and Levinson L Evaluation of Therapeutic Substances Employed for the Relief of Bronchospasm Ann Allergy 5 317 1947
169 Segal M S Beakey J F Bresnick E and Levinson L A Comparative Study of the Action of Various Sympathomimetic Amine Aerosols in Counteracting the Dyspnea and Bronchospasm Induced by Histamine and by Acetyl Beta Methylcholine Bull New England M Center 10 21 1948; J Allergy 20 97 1949
170 Segal M S Levinson L Bresnick E and Beakey J F Evaluation of Therapeutic Substances Employed for the Relief of Bronchospasm 6 Aminophyllin J Clin Investigation 28 1182 1949

171 Segal M S and Ryder C M Penicillin Aerosolization in Treatment of Serious Respiratory Infections Preliminary Report *New England J Med* 233 747 1945
172 Segal M S and Ryder C M Penicillin Aerosol in Management of Lobar Pneumonia Bronchiectasis Lung Abcess and Infective Bronchial Asthma Bull *New England M Center* 7 279 1945
173 Segal M S and Ryder C M Pencillin Inhalation Therapy *New England J Med* 236 132 1947
174 Segal M S Levinson L and Miller D Penicillin Inhalation Therapy in Respiratory Infections *J A M A* 134 762 1947
175 Selye H Studies on Adaption *Endocrinology* 21 169 1937
176 Selye H General Adaptation Syndrome and Diseases of Adaptation *J Clin Endrocrinol* 6 117 1946
177 Sherman W B Drug Allergy *Am J Med* 3 586 1947
178 Solomon H A and Somkin E Improved Method of Obtaining Sustained Controlled Hyperpyrexia with Triple Typhoid Vaccine *Am J M Sc* 203 736 1942
179 Spain W C and Cooke R A Specific Hypersensitiveness Familial Occurrence of Hay Fever and Bronchial Asthma *J Immunology* 9 521 1924
180 Spain D M Handler B J Chronic Cor Pulmonale Sixty Cases Studied at Necropsy *Arch Int Med* 77 37 1946
181 Staub H Die Adrenalin Histamin Regulation mit Beitrag zum Antistin mechanismus *Schweiz med Wchnschr* 76 818 1946
182 Stevenson I P Bronchial Lavage for Bronchiectasis A Preliminary Report of a Simplified Technique *Am Rev Tuberc* 56 279 1947
183 Stieglitz E J The Histologic Detection of Iodides *J Pharmacol & Exper Therap* 22 89 1924
184 Sweatman C A Treatment of Bronchial Asthma and Hay Fever with Cyclopropane *J South Carolina M A* 37 291 1941
185 Talbot T R Jr Quimby E H and Barach A L A Method of Determining the Site of Retention of Aerosols Within the Respiratory Tract of Man by the Use of Radioactive Sodium *Am J M Sc* 214 585 1947
186 Thieme E T and Sheldon J M Correlation of Clinical and Pathologic Findings in Bronchial Asthma *J Allergy* 9 246 1938
187 Tiffeneau R and Beauvallet M Epreuve de bronchoconstriction et de bronchodilatation par aérosols Emploi pour le dépistage la mesure et le contrôle des insuffisances respira

toires chroniques *Bull Acad de med Paris 129* 165 1945
188 Titche L L Anesthesia in Tracheo Bronchial Procedures *Dis of Chest 13* 452 1947
189 Tuft L and Levin N M Studies of the Expectorant Action of Iodides *Am J M Sc 203* 717 1942
190 Unger L and Gordon B F Bronchial Asthma (IV) Critical Review of Literature *Ann Allergy 6* 159 1948
191 Unger L and Wolf A A Treatment of Bronchial Asthma a Survey of the Value of Treatment in 459 Cases During Twenty Years *J A M A 121* 325 1943
192 Unger L Pathology of Bronchial Asthma with Five Autopsy Reports *South M J 38* 513 1945
193 Van Wijk A M and Patterson H S Percentage of Particles of Different Sizes Removed from Dust laden Air by Breathing *J Indust Hyg and Toxicol 22* 31 1940
194 Villaret M Vallery Radot P Justin Besancon L and Claude F Recherches Préliminaries Sur les Crises Provoquées Chez les Asthmatiques par Certains esters de la Choline *Compt rend Soc de Biol 116* 1343 1934
195 Villaret M Vallery Radot Justin Besancon L and Claude F Crises Asthmatiformes Expérimentales Provoquées par L ad ministration de Vagomimetiques Après Irritation Pulmonaire *Compt rend Soc debiol 124* 1308 1937
196 Waldbott G L Emergencies in Allergist s Practice *J A M A 128* 1205 1945 reply to Engelesher *129* 979 1945
197 Waldbott G L Does Routine Treatment of Asthma Need Revision? *Ann Allergy 5* 126 1947
198 Waldbott G L Is There An Intrinsic Asthma? *Ann Int Med 26* 863 1947
199 Waldbott G L and Ascher M S Role of Accidental Puncture of Veins in Production of Allergic Shock *Ann Int Med 9* 1232 1936
200 Walker I C A Clinical Study of 400 Patients with Bronchial Asthma *Boston M & S J 179* 288 1918
201 Winer B Beakey J F and Segal M S A Clinicopathologic Study of Bronchial Asthma with Consideration of its Relationship to the General Adaptation Syndrome *Ann Int Med* in Press
202 Wittich F W The Present Day Concept of Allergic Phenomena Medical Briefs Frederick Stearns and Co 2 1 1946
203 Wittich F W Bacterial Allergy Regional Spring Course *American College of Allergists* Kansas City Kan May 5 1947

204 Yonkman F F Adrenergic Potentiation A Pharmacodynamic Effect Associated with Antihistaminic Agents *Am J Digest Dis*, *14* 360 1947

205 Yonkman F F and Mohr F L An Approach to the Problem of Epinephrine Fastness *Ann Allergy 7* 60 1949

205a Yonkman F F Levinson L and Segal M S An Approach to the Problem of Epinephrine Fastness *Am J Digestive Diseases* in Press

206 Editor Voice Changes from Inhalation of Helium Oxygen Queries and Minor Notes *J A M A 113* 706 1939

207 Standards of Effective Administration of Inhalational Therapy By the Committees on Public Health Relations of the New York Academy of Medicine *J A M A*, *121* 755 1943

208 Gilman A The Pharmacology of Drugs Used in Allergic Conditions *J Allergy 19* 281 1948

INDEX

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WITH
Severe Bronchial Asthma

BY MAURICE S. SEGAL, M.D.

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